TREATMENT OF CANCER AND ALLIED DISEASES

SECOND EDITION

Volume I: Principles of Treatment

TREATMENT OF CANCER AND ALLIED DISEASES

Second Edition

Volume I Principles of Treatment

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Jointly dedicated to the late

JAMES EWING

for his outstanding leadership in cancer research his continual encouragement of co workers and his profound influence in enhancing the recognition of neoplastic diseases as a field of unified special endeavor

and to

JOHN D ROCKEFELLER, JR

for his devotion to the cause of medical research and education and especially for his establishment in the Memorial Hospital of the Rockefeller Fellowships for training physicians in clinical cancer therapy

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Foreword to the Series

Each year in the United States of America approximately 450 000 people are diagnosed as harboring cancer while 40 million others now healthy will develop cancer during their remaining lifetime * These present and future patients must be treated The treatment will vary from procedures that are aimed at being curative through the entire spectrum of medical therapy to the terminal care of the patient dying from cancer

More than five thousand medical journals are published throughout the world There are more than four thousand articles a year dealing with cancer in the English language literature alone It is obvious that no one person can digest and assimilate all the information contained in these articles The growth of this second edition of *Treatment of Cancer and Allied Diseases* from the original three volumes to its present *nine* volumes has occurred in an attempt to create a reservoir of existing knowledge of therapy on which any physician can easily draw The object is to bring together in one authoritative work the tremendous mass of detailed information concerning the technics of all phases of cancer therapy in current use The care of the patient is emphasized throughout and palliative procedures are presented with the same emphasis given to measures aimed at cure

The treatment of cancer is based upon two main factors (1) the histogenetic classification of the tumor and (2) the clinical setting of the tumor—that is its location and extent Ewing demonstrated that the histogenetic classification of tumors allows a breakdown of tumor types and permits an understanding of the natural history of each specific tumor His monumental work presented the first great attempt to divide and conquer cancer

PLAN AND SCOPE

There are nine volumes in the series divided on a regional basis within which framework are presented the treatment procedures best suited for a given histologic type of cancer Volume I discusses principles of cancer therapy and includes such subjects as the prevention of cancer the technics of biopsy the preoperative and postoperative care of the cancer patient the indications for technics and accomplishments of radiation therapy etc Volume II describes the treatment of tumors of the nervous system Volume III the treatment of tumors of the head and neck Volume IV the treatment of tumors of the breast chest and esophagus Volume V the treatment of tumors of the gastrointestinal tract Volume VI the treatment of tumors of the female genitalia Volume VII the treatment of tumors of the male genitals and of the urinary system Volume VIII the treatment of tumors of the soft somatic tissues and of the osseous system and Volume IX the treatment of tumors of the skin and of lymphomas and allied diseases

* American Cancer Society personal communication [illegible]

The present series correlates contributions from recognized authorities on neoplastic diseases from prominent cancer centers and treatment institutions in many parts of the world At all times the editors have attempted to present the time proved methods of cancer therapy There is no easy way to measure the efficiency of a given therapeutic modality The generally accepted criterion today is the so called definitive five year cure rate obtained for a given form of cancer by the institution of a given treatment method Accordingly only those measures that have been utilized over a prolonged period so that their accomplishments can be properly evaluated are presented in detail The editors however have not been unmindful of the newer and experimental methods and the reader will find them appropriately discussed

Wherever controversy exists as to the best method of treatment the editors have attempted to achieve a perspective by including the different modalities applicable to a given cancer In introducing several of the chapters forewords have been included to give the reader a broad perspective of cancer therapy in the special field discussed

The aim throughout has been to secure a work that is practical Although the text comprises a total of nine volumes there will be found little deviation at any point from the general title of applied therapy Except insofar as an immediate and direct bearing on treatment could be demonstrated all data concerning etiology pathology symptomatology differential diagnosis or research have been excluded Despite the size of the published work it has been necessary to exclude as much if not more material from the original submitted manuscripts than was utilized in the final printing We are grateful to the individual authors for their consideration and tolerance with regard to these condensations Because of the arduous and prolonged editorial task each of the over five hundred contributors was given the opportunity to review his manuscript and to include new developments so that on publication each volume reflects the authors current thinking

In a work of such scope it is but natural that certain conflicts of opinion and a limited amount of reiteration should occur This has insured that all sides of the major problems of treatment are given full consideration this advantage to the reader is exemplified, for instance, in the presentation of the difficult subjects of management of metastatic carcinoma to the cervical lymph nodes, cancer of the cervix cancer of the larynx, as well as other topics The reader is urged to view the clearly identified contributions of each author as well as the editorial comments, as expressions of individual conviction based on personal experience except where these are accompanied by an assessment of factual data

The cancer patient as a rule first consults a family physician or a general medical clinic therefore the first physician who suspects or proves the presence of cancer plays an important role in a therapeutic emergency in regard to time of treatment choice of treatment and the mental attitude with which the patient approaches the necessary therapeutic steps This series of manuals of treatment accordingly is directed at all who play a part in the management of cancer and not at the cancer specialist alone

CHANGES IN THERAPY

This second edition is an entirely rewritten and reorganized work The vast strides made in cancer therapy in the past two decades and the increased knowledge of all phases of the cancer problem have demanded a complete rewriting with deletion of those procedures now either obsolete or considered to be irrelevant to the direct problem of tumor treatment

Advances in our knowledge of anatomy and physiology are reflected in the more radical operative procedures described in these volumes e g bilateral neck dissection radical pneumonectomy right hepatic lobectomy pelvic exenteration and major exarticulations Intrathoracic cancer has increased steadily in incidence through the years since the first edition and pari passu has followed a corresponding betterment in chest surgery From sixty eight pages in the first edition coverage has grown to an entire volume largely devoted to this aspect of cancer therapeutics

Attention is directed throughout all volumes to the proper preoperative and postoperative care of patients subjected to surgical

removal of their cancers Technics of anesthesia are discussed Authorities in these fields present these important aspects of cancer treatment in separate chapters These subjects have therefore been omitted from the chapters dealing with surgical technics except where certain procedures require special consideration of anesthesia and of preoperative and postoperative care

The great advances in radiologic technic and the use of these complex and powerful tools aimed at controlling cancer are presented in terms of therapy

HORMONAL THERAPY

The observation that hormonal balance influences human cancer is most significant dispelling the theory that the cancer is an absolutely autonomous growth and indicating that it is under certain body controls This concept opens up great vistas for further investigation into the biologic behavior of cancer in addition to providing important measures for treating patients bearing certain forms of neoplasm The use of hormones for the growth control of specific cancers and the ablative hormonal surgery such as orchidectomy oophorectomy adrenalectomy and hypophysectomy are discussed in these volumes because of their important roles in the palliative management of certain cancers

CHEMOTHERAPY

The discovery of a cancer cure by means of chemotherapy is the fervent hope of both the public and the medical profession The ultimate cure of cancer some day by methods other than surgical extirpation or radiation sterilization is a probability, but to predate the time for such a discovery is not only faulty logic but dangerous propaganda The regression of cancers in mice or the temporary amelioration of acute leukemia by chemotherapy is evidence of progress but these should not be exploited beyond their actual significance At this writing *no known human cancer can be cured by chemotherapeutic measures*

Chemotherapy as developed and practiced during the past fifty years has made important contributions to the management of cancer viz

1 Tools for research into the nature of cancer with a mustering of all the chemical sciences including immunology endocrinology enzymology and the chemical identification of antitumor derivatives of bacteria and viruses

2 The curbing of the progression of certain cancers and the marked palliation in patients harboring them (leukemia and prostatic and breast carcinoma)

3 A measurable relief from suffering and the prolongation of life in comfort for patients wtih incurable cancer which have altered the philosophical attitudes concerning this disease Cancer even when beyond the stage of complete eradication need no longer be regarded as the hopeless miserable disease that it has been but may be considered with such conditions as heart disease cirrhosis chronic nephritis and others of which the patient is never cured but with which he may live pleasantly for prolonged periods

END RESULTS OF TREATMENT

A reliable presentation of end results has been stressed in all the volumes There may be a margin of error in the classification of a regional or histologic type of cancer as operable or inoperable because of the variable factors in the pronouncement of a given cancer as nonresectable by any surgeon These are first the condition of the patient as regards his age the coexistence of degenerative diseases and the complications attendant on the presence of the cancer second the extent of the disease meaning the degree of local or organic involvement the specific organ or tissue implicated the extension to and the incorporation of neighboring viscera by the cancer and metastases to regional and distant sites and third the surgical philosophy moral point of view courage and experience of the surgeon

The concept of cancer as an incurable disease is widely accepted in spite of the educational efforts of the American Cancer Society and other organizations The hopelessness of a given case may be recognized by the physician at the initial examination but the published figures of thousands of cancer cures should encourage a more hopeful attitude toward cancer as a whole

DEFINITION OF PALLIATIVE TREATMENT

Palliative treatment is eagerly accepted for all incurable diseases except cancer its employment for cancer generally is regarded with skepticism and without enthusiasm by the patient and his family A diagnosis of arteriosclerosis chronic nephritis diabetes mellitus myocarditis coronary vascular disease osteitis deformans and many other degenerative conditions is accepted with equanimity, fortitude and optimism by the majority of patients yet the end results of treatment show that they are all *incurable* diseases These patients usually ask of their physicians only that treatment that lies within the realm of possibility hoping that it will successfully arrest the process for the time being avoid the complications and disabilities attendant on the disease and prolong life in comfort If the diagnosis be cancer however nothing short of a guarantee of cure seems to suffice and an expression by the physician of a reasonable doubt concerning ultimate cure frequently leads to a profound and unreasonable reaction and a refusal of all treatment—either surgical or radiologic

The medical profession has not been faultless in fostering this attitude Accent has been on cure rather than on palliation Published figures on the end results of treatment usually present the percentages of so called five year cures or survivals without recurrence for five years The great group of cases in which life has been prolonged for less than five years does not receive the attention it deserves

The prolongation of life itself is of course not the only measure of palliation No one wishes to live longer in order to suffer more The objectives of palliative efforts are the relief of pain and discomfort the healing of ulcerated lesions the lessening of hemorrhage and infection the repair of certain pathologic fractures the healing of metastases in bone the eradication of cough and dyspnea the restitution of sleep and the delay in spread of the cancer among many others Appropriate irradiation for example might give relief of some symptoms without prolonging the life of the patient None would deny that such efforts are worthwhile

The editors paradoxically hope that these volumes may soon become obsolete with the discovery of more efficient means of curing cancer such as a chemotherapeutic remedy or better yet by the creation of an immunity against the disease In the meantime these manuals of present day therapy are offered with the wish that the best treatment plan now available can be instituted for any patient bearing any form of cancer

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New York

Preface

In this first volume of the series *Treatment of Cancer and Allied Diseases* the editors have tried to approach the subject in a logical manner with preliminary emphasis on cancer prevention immediately followed by suggestions for the organization of adequate facilities for the detection of cancer Because the pathologic features of a given cancer have a direct influence on its behavior and response to treatment chapters are devoted to specific diagnosis and classification in terms of microscopic grading biopsy examination of exfoliated cells and tissue cultures Tumors are classified into Grades I to IV Grade I being the more differentiated and Grade IV the more anaplastic based on the work of Broders (1920) However the extent of the cancer at the time of its diagnosis is also important from a prognostic standpoint and the reader will find a discussion of criteria utilized to grade the malignant quality of cancers the extent of infiltration into the surrounding parenchyma the presence or absence of encapsulation the quantity and character of host reaction and the evidence and distribution of metastases With certain clinical indexes such as age menstrual status and pregnancy these grading features offer important signposts for the prediction of prognosis following treatment The formal biopsy has become an obligatory pretherapeutic procedure and methods for aspiration or punch biopsy are presented Technics for the collection and examination of exfoliated cells for the cytodiagnosis of cancer are presented

The ancients destroyed cancer either by cutting it out or by burning it out The only methods of curing human cancer today are by surgical extirpation of the growth or its destruction by ionizing radiations the basic principles are essentially the same as those of the ancients but the methodology is more refined In the section on surgery an attempt is made to afford guidance for the safe conduct of a patient through the ordeal of a surgical procedure Principles of preoperative and postoperative care are adumbrated as are the control of concomitant metabolic or degenerative diseases Particular attention is paid to estimation of the operative risk The chapter on vascular surgery points out the major achievement of replacement by grafts of excised segments of critically important blood vessels

As a cure for cancer radiation therapy is second only to surgery Irradiation is superior for the curative treatment of certain cancers and is of far greater importance in offering palliation to patients suffering from widespread dissemination of cancer In this book the reader will find a logical discussion of all phases of irradiation from the physical basis of radiation therapy and the radiosensitivity of tumors through the technics of clinical application of low voltage short distance medium voltage supervoltage moving field and betatron x ray therapy Sections are devoted to the clinical uses of radium and of radioactive isotopes The methods of applying radium the radium element pack, and the

multiple source radium beam are discussed in separate chapters The production of radio active isotopes such as radioactive iodine and radioactive phosphorus is discussed as are the clinical applications of systemic radioactive isotopes small sources of radioactive gold iridium and cobalt and the use of the radio active cobalt beam (cobalt teletherapy)

The general care of the patient with an in operable cancer is discussed in detail including the use of hormonal therapy and chemotherapy for modifying the growth of certain cancers in addition to ameliorating symptoms The proper methods of reporting end results of cancer therapy are also discussed here

In this volume the editors have tried to adhere to the principles of cancer treatment describing those methods used for cure as well as those aimed at palliation and leaving it to subsequent volumes in the series to discuss the therapy of specific types of cancer within a framework of regional division

G T P
I M A

Acknowledgments

It is a duty and a pleasure to acknowledge with appreciation our indebtedness to the many authorities who have made this book possible The quality of their chapters and their co-operative spirit have contributed to the completion of this introductory volume the first in an ambitious encyclopedia planned to encompass the entire scope of therapy of all neoplastic diseases

The superior medical illustrations contribute greatly to the value of the text We express our gratitude to each of the medical illustrators and to our own medical artist Mr Alfred Feinberg

We join the authors in acknowledging the generous co-operation of the many authors journals and publishers who freely permitted the use of graphic and statistical material Specific acknowledgments are given throughout the text

Our research assistants Miss Mildred Ashley and Miss Sybil Harris have been most assiduous and competent in the assemblage of statistical and referential data

Miss Ebba M Rogstad our editorial associate tirelessly reviewed the manuscripts critically read the galley and page proofs and indexed this volume

The American Cancer Society Inc has given a substantial grant in aid which has made possible the presentation of colored illustrations in these volumes

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Finally we are indebted to Mr Paul B Hoeber our publisher for his zealous and enthusiastic guidance

G T P
I M A

Organization

CHAPTER 1

The Prevention of Cancer

W C Hueper

The preventive approach for controlling cancer should assume a much more important role than it does at present because of the relative inadequacy of existing methods of treatment

1 MAGNITUDE AND SOCIAL IMPORTANCE OF CANCER

a There were approximatly 600 000 diag nosed cases of cancer in the United States during 1949

b About one third of these cancer patients or about 200 000 died during the year

c Approximately 45 per cent of all cancer deaths are of persons between the ages of twenty five and sixty five years which is the most productive period of life

d A considerable increase in the frequency of certain cancers (cancer of lung leukemia) has occurred

e With the rapidly increasing shift in the age distribution toward older age groups (in 1900 about 4 per cent of the population were sixty five years and older in 1935 this frac tion stood at 6 per cent and it is estimated that it will be 11 per cent in 1980) a pro gressively larger number of people will reach an age in which cancer is most frequent (more than 50 per cent of all cancer deaths involve persons sixty five years and older) It has been estimated that the number of annual cancer deaths will reach about 300 000 by 1980

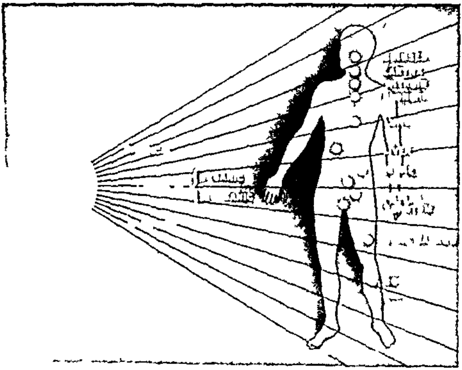


Fig 1 1 Environmental causes of cancer and organs affected

TABLE 1 1 —OCCUPATIONAL CARCINOGENS THEIR ROUTE OF EXPOSURE AND THEIR TARGET ORGANS

General type	*Specific type*	*Route of exposure*	*Target organ*
Chemical Carcinogens Organic chemicals aromatic polycyclic heterocyclic	Benzol	Cutaneous Respiratory	Blood forming organs (leukemia lympho sarcoma)
	Beta naphthylamine Benzidine 4 Aminodiphenyl Auramine	Respiratory Cutaneous Alimentary	Urogenous organs (bladder ureter kidney) Lung? intestine?
	Coal tar pitch asphalt tar oil creosote oil anthracene oil lamp black lignite tar and paraffin oil	Cutaneous Respiratory	Skin Lung
	Synthetic hydrogenated coal oil and tar (Bergius)	Cutaneous	Skin
	Shale oil and paraffin oil	Cutaneous Respiratory	Skin Larynx
	Petroleum fuel oil diesel oil lubricating oil and grease cutting oil carbon black asphalt tar coke crude paraffin oil	Cutaneous Respiratory	Skin Lung
Aliphatic	Isopropyl oil	Respiratory	Nasal sinus larynx lung
	Mustard gas	Respiratory	Lung larynx?
Chemical carcinogens Inorganic chemicals	Arsenic	Cutaneous Ingestive	Skin
		Respiratory	Lung
	Nickel	Respiratory	Nasal cavity nasal sinus lung
	Chromium	Respiratory	Lung
	Asbestos	Respiratory	Lung
Physical carcinogens	Ultraviolet radiation	Cutaneous	Skin
	Ionizing radiation X radiation	Cutaneous Transcutaneous	Skin Connective tissue Bone Blood forming organs
	Radioactive radiation (alpha beta and gamma radiation)	Cutaneous Transcutaneous Respiratory Ingestive Parenteral	Skin Connective tissue Blood forming organs Nasal sinus Lung Bone Liver
Parasite carcinogens	Schistosoma haematobium	Cutaneous	Bladder

TABLE 1 2—POTENTIAL ENVIRONMENTAL HUMAN CARCINOGENS

Agent	*Site of tumor*	*Type of exposure*	*Species*	*Types of human contact*
Estrogens natural synthetic	Breast Lymph nodes Uterus Hypophysis	Parenteral Cutaneous Oral	Mouse Rat Rabbit Guinea pig	Manufacture Dietary additive Cosmetic ingredient
Carbon tetrachloride	Liver	Oral	Mouse	Industrial solvent Degreasing agent Dry cleaning agent Fire extinguishing agent Manufacture Production of freon Grain fumigant Extractive of oils
Chloroform	Liver	Oral Parenteral	Mouse	Manufacture Anesthetic Solvent and extractive of oils resins rubber waxes iodine alkaloids Ingredient of lacquer floor polish cleaning fluid Production of artificial silk plastics
DDT	Liver	Oral	Rat	Manufacture Insecticide Food contaminant
Tannic acid	Liver	Parenteral	Rat	Ingredient of foodstuffs (fruits wine coffee and tea) Medicinal agent Tanning agent
Thiourea and derivatives	Liver	Oral	Rat	Citrus fruit preservative Medicinal agent
Dulcin	Thyroid Liver	Oral	Rat	Manufacture Sweetening agent
Diethylene glycol	Bladder	Oral	Rat	Antifreeze Intermediate in explosive manufacture Softener of lacquer inks wood stains glue textiles Humectant tobacco
Methylated naphthalenes	Skin	Cutaneous	Mouse	Vehicle of insecticides
Bergius coal oils tars	Skin Subcutaneous tissue	Cutaneous *Parenteral*	Mouse	Manufacture *Fuel* Lubricants Plastic production Petrochemical

TABLE 1 2 *(Continued)*

Agent	*Site of tumor*	*Type of exposure*	*Species*	*Types of human contact*
Fischer Tropsch coal oils tars waxes greases	Liver	Cutaneous Parenteral	Mouse	Manufacture Fuel Lubricants Petrochemical
Light green SF Brilliant blue FCF *Fast green FCF*	Subcutaneous tissue	Parenteral	Rat	Textile dyes Food and cosmetic dyes
Butter yellow	Liver	Oral	Mouse Rat	Food dye (Orient) Gasoline and flare dye
Cellophane Polyethylene Polyamide Bakelite	Subcutaneous	Parenteral	Rat Mouse	Film fiber plastic industrial manufacture and uses Wrapping material Medicinal agent
Beryllium	Bone	Parenteral Respiratory	Rabbit Rat	Metal alloy x ray tube phosphor manufacture Refractory vessels Atomic energy production
Selenium	Liver Thyroid	Oral	Rat	Soil contaminant Coloring matter of glass ceramics paint rubber Metal alloys Rubber accelerator Photoelectric apparatus Decolorizer Fireproofing agent Medicinal agent

II ETIOLOGY OF CANCER

The causation of the great majority of human cancers is unknown

Predisposing Causes

a *Hereditary factors* provide a predisposition to cancer development in a few types of cancers (cancer of skin in xeroderma pigmentosum cancer of intestine in familial intestinal polyposis familial retinoblastoma neurosarcoma in familial neurofibromatosis)

b *Racial factors* (fair complexion) seem to be associated with an increased susceptibility to cancer of the skin upon prolonged contact with solar rays and cancerigenic products obtained by the distillation of coal and petroleum

Precipitating Causes

a *Acute physical or chemical trauma* may precipitate the development of cancer in a tissue that has previously been prepared by the action of specific cancerigenic agents

b *Chronic irritation* which per se and while nonspecific does not cause cancer may accelerate the development of cancer in tissue exposed to specific cancerigenic agents

Specific Causes

There exists a relatively small but nevertheless impressive number of specific environmental agents mainly of an occupational nature that have been shown to cause cancer of various organs in man Table 1 1 summarizes some of the salient facts concerning *these* agents (Figure 1 1)

A growing number of chemicals of industrial and/or general environmental importance that have elicited malignant tumors in various species of animals and that therefore may be suspected of having similar effects *on man* has been demonstrated These potential environmental cancerigens are listed in Table 1 2

Table 1 3 lists a number of contacts and conditions of a rather vague nature that dis

TABLE 1 3—ILL DEFINED ENVIRONMENTAL CANCERIGENIC AGENTS

Cancerigenic agent	*Type of exposure*	*Site of cancer*
1 Parasites		
Schistosoma haematobium	Ingestion	Bladder
Schistosoma mansoni	Skin penetration	Liver?
Schistosoma japonicum		Intestine?
2 Dietary imbalances		
Iodine deficiency		Thyroid
Vitamin B complex deficiency		Oropharynx
Vitamin B complex and protein deficiency		Liver
3 Vegetable mineral		
Mixtures		
Betel nut Tobacco		Mouth
Lime Buyo leaf		Lip
Quid (Tobacco extractives)		Cheek
Tobacco Lime		
(Khaini) Quid (Tobacco extractives)		Lower lip
4 Indeterminate agents		
Chronic alcoholism (Contaminants or solutes of alcohol)		*Esophagus*
Kangri Kairo Kang Thermic burns		
(Thermic carbonization of tissue with tar formation? Soot?)		Skin
Chutta (Smoking cigars in inverted position) (Tar? Burns?)		Mouth
Tobacco smoking (Tar arsenic?)		Mouth Lip Larynx Lung Skin
Dhoti loin cloth (Soot? Disintegrated sebum?)		
Phimosis		
Noncircumcised penis (Disintegrated smegma?)		Penis

play causal relations to certain human cancers

Since the liver is apparently involved in the detoxication of endogenous and exogenous cancerigens defective liver function may favor the action of the development of cancers in organs other than the liver The occurrence of gynecomastia in the presence of liver cirrhosis which has been attributed to an impaired metabolic degradation of estrogens may be cited as an illustration of such potential interrelations

III ETIOLOGY—SPECIFIC CANCER DIAGNOSIS

Table 1-4 lists a series of exposure stigmata which may either be precancerous or pericancerous

IV PREVENTIVE MEASURES

Levels of Prevention

Preventive measures may be applied at three different levels of cancer development

a Primary prevention aims at elimination of the production of cancerigenic agents in the internal or external human environment or at the reduction or prevention of exposure of man to environmental exogenous or endogenous cancerigenic agents This procedure is only sporadically practiced at present

b Secondary prevention or prophylaxis has as its goal the discovery eradication or neutralization of all predisposing or precancerous factors occurring in persons who are or previously have been exposed to cancerigenic agents

TABLE 1 4—PRECANCEROUS AND PERICANCEROUS REACTIONS TO ENVIRONMENTAL CARCINOGENS

Reactions	*Etiologic agents*
SKIN	
Alopecia Spotty loss of hair	Arsenic ionizing radiations (radioactive substances x radiation)
Atrophy Skin grossly thinned and glistening in patches associated with keratotic areas	Pitch tar asphalt petroleum radioactive substances x radiation ultraviolet radiation solar rays
Eczema Dry seborrheic patches on skin	Arsenic asphalt pitch soot tar
Keratosis Flat discrete scaly area on skin with raised pearly borders Usually on parts of skin exposed to carcinogen but may occur in unexposed parts particularly about sweat glands with arsenic	Anthracene arsenic asphalt creosote crude mineral oil paraffin pitch soot tar radioactive substances ultraviolet radiation x radiation
Hyperkeratosis Rough fissured keratotic plaques with small hard wartlike horns usually on hands and soles May become nodular and ulcerate	
Verrucae Hornlike hyperkeratosis	
Ulceration Breakdown of keratotic lesions Chrome holes	 Arsenicals Chromates chromic acid
Leukoderma Patches of subnormal melanin pigmentation	Anthracene arsenic asphalt creosote crude mineral oil paraffin pitch tar nonionizing and ionizing radiations (radioactive substances x radiation ultraviolet radiation solar radiation)
Leukomelanoderma Patches showing increased pigmentation and patches showing subnormal pigmentation of skin Most common in areas of highest pigmentation and may involve oral mucosa	
Melanoderma Patches of increased pigmentation	
Scleroderma Dry scaly parchment like skin with enlarged pores associated with leukomelanoderma	Crude mineral oil paraffin oil ionizing radiations (radioactive substances x rays ultraviolet rays solar rays)
NASAL PASSAGES	
Papillomas and polyps Growths in antrum ethmoid cells and turbinates Nasal septum perforations	Isopropyl oil nickel chromates arsenicals
BLADDER	
Hemorrhage submucosal Varying size with telangiectasis Located mainly in trigone and about ureteral orifices	Benzidine beta naphthylamine and derivatives Schistosoma haematobium
Papillomas Polypous or villous pedunculated or sessile Often multiple about trigone and ureteral orifices	

TABLE 1-4 *(Continued)*

Reactions	*Etiologic agents*
EYES	
Papillomas	
Pedunculated Develop mainly on lids oc casionally on eyeball	Arsenic asphalt creosote crude mineral oil pitch tar ionizing radiations ultraviolet rays
BONE	
Chronic periostitis	
Thickening of periosteal tissue necrosis of bone	Ionizing radiations (x rays radioactive substances) beryllium?
BONE MARROW HYPOPLASIA	
Blood dyscrasias	
Hyperplasia and metaplasia aplastic anemia thrombocytopenia leukopenia monocy tosis erythrocytosis leukocytosis leu kemoid reactions	Benzol and derivatives ionizing radiations (radio active substances x rays)
LUNGS	
Pneumoconioses and pneumonia	
Asbestosis lipoid pneumonia chronic chemical pneumonia	Asbestos arsenic tar soot mineral oil mist chrome salts nickel
BREAST	
Painful swollen breasts	Estrogenic chemicals
Glandular hyperplasia	
LIVER	
Cirrhosis	Aromatic azo compounds?
Adenomatoid hyperplasia	Vitamin B complex and protein deficiency
OROPHARYNX	
Plummer Vinson syndrome	Vitamin B complex deficiency
Leukoplakia	
THYROID	
Endemic adenomatoid goiter	Geologic and dietary iodine deficiency

c Those measures found at the third level deal with an already established cancer and therefore are restricted to modifying the natural course of a manifest disease through appropriate diagnostic and therapeutic procedures In addition to attempting the improvement of the prognosis of cancer the measures used at the third level are aimed at the prevention of serious complications residual disability and permanent incapacitation They are thus more a part of a rational and effective cancer therapy and less within the province of cancer prevention proper

Possible Extent of Prevention

HEREDITARY FACTORS

The future occurrence of the relatively few cancers of recognized hereditary origin can effectively be reduced if individuals with such tendencies are properly appraised of the situation and are urged not to have progeny

RACIAL FACTORS

Fair-complexioned persons should not be permitted to work in operations where they are exposed to cancerigenic tars pitches asphalts and other petroleum distillates and oils or to intense solar radiation unless adequate protective measures are taken

ENVIRONMENTAL AND OCCUPATIONAL FACTORS

a Occupational cancer hazards can completely or almost completely be removed by the institution of suitable preventive and prophylactic measures for all workers engaged in the primary production or handling of the

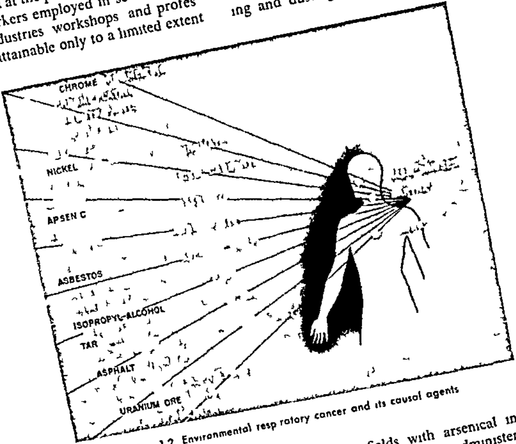


Fig 1 2 Environmental resp ratory cancer and its causal agents

various cancerigenic agents This goal can not be achieved at the present time to the same degree for workers employed in secondary or consuming industries workshops and professions and is attainable only to a limited extent whenever industrial cancerigens reach the general population in the form of consumer goods or industrial wastes

A few citations of actual conditions may help to illustrate this point

A cancerigenic arsenic hazard exists for the miners who mine arsenic containing ores (copper silver zinc lead) The hazard extends from there to workers in smelters where the bulk of the white arsenic is obtained as a by product of metal ore smelting From there arsenic gets to the consuming industries that use it in the production of pesticides weed killers glass lead base alloys dyestuffs cattle and sheep dips wood preservatives poison bait chemical warfare gases and in the Thylox purification of industrial gases The list of occupations in which these and other arsenicals are handled is extensive Since arsenicals at some smelters are freely released into the atmosphere or remain in the slag heaps there exists the danger of a contamination of drinking water supplies from these sources causing the development of an endemic arsenicism A similar result may ensue from the liberal spraying and dusting of vineyards orchards and cotton fields with arsenical insecticides Finally arsenicals are administered to man for therapeutic purposes or may be consumed with contaminated foodstuffs liquor tobacco and candies Cancers of the skin and possibly also of the lung and liver have been traced to most of these various exposures to arsenic

A similar centrifugal spread of exposure may be noted for the tarry products obtained by the incomplete combustion of coal Workers employed in gasworks and coke ovens where the bulk of the industrially important tar is produced may sustain skin contact with this material or may inhale hot tar fumes and develop cancer of the skin or of the lung depending on the type of exposure The tar is then fractionated into tar oils creosote pitch and anthracene oil in addition to lighter and more volatile products which with the exception of benzol are usually noncarcinogenic These fractionation products are either used as they are for a great number of purposes or are

processed and transformed into well defined chemical compounds forming together with petroleum derivatives the main source material for the modern organic chemical and pharmaceutic industry Since the entire list of products entering into the manufacture of tar pitch asphalt creosote oil anthracene oil mineral waxes and related materials is very long only a selection of the most common uses can be given These are enamels paints inks varnishes roof coating material cement mortar putty shingles tiles roofing paper waterproofed paper, felt textiles nets cords and panels acoustic blocks compositions and felts calking material wood preservatives road construction material electric appliance and wire insulation material casting molds battery boxes cork composition ditch dike and jetty protectives leather composition linoleum foundry cores friction tape pipe coating tree surgery paste lubricants cable splicing compounds clay pigeons fuel wall boards and many other products

The application of radioactive luminous paint to numerous devices of warfare was practiced by many hundreds of persons during the late war and is still an operation in which a considerable number of workers are engaged Radioactive hazards have been introduced lately into the pharmaceutic and other industries through the use of radioactive isotopes employed in the production and application of tracer substances Radioactive substances are moreover handled in the production of radio tubes electrostatic eliminators gas mantles radium type vacuum gauges and nickel polonium alloy spark plugs In this connection it is interesting to note that a considerable amount of the tremendous quantities of radium used in luminous paint is unaccounted for since markers dials and rope carrying the radioactive material have occasionally found their way into the hands of persons not qualified to dispose of them properly While thus on the one hand a certain degree of environmental radioactive hazards may have come to parts of the population not generally expected to sustain such exposures there remains the probability that the cancer hazard from contact with radioactive dust and gases starts with the mining of the ore if the experiences made with lung cancers in miners of such ores in Czechoslovakia and Germany should prove to be of general application Similar actual and potential cancer hazards are connected with the production and the use of atomic energy

b An effective control of environmental cancer hazards related to habits is at present most difficult because of educational sociologic economic and political implications and complications

For instance it would be a very uncertain venture to try to dissuade the inhabitants of India Thailand the Philippine Islands and other Asiatic countries to discontinue the widespread habit of chewing betel nut quids or Khaini quids which is causally related to cancer of the oral cavity and lip If it should definitely be shown that smoking is one of the main causes of cancer of the respiratory organs it would not be easy to induce the people of the Western World to give up the smoking of tobacco

The prevention of primary cancer of the liver among the defectively fed peoples of Africa and Asia depends mainly upon adjustments in the economic field Likewise an effective suppression of Schistosoma haematobium infections among the Egyptian fellahs to reduce the incidence of bladder cancer among this population group depends predominantly on nonmedical measures

c Likewise the occurrence of medicinal cancers resulting from the medical use of ionizing radiation arsenicals tars benzol and aromatic chemicals cannot entirely be suppressed because of the special indications for which these agents are used and of insufficient knowledge as to the cancerigenic level at which they may elicit cancers in different individuals

Measures Useful in Prevention

Even the limited amounts of information existing on the causes of human cancer are not properly appreciated and utilized The average medical history of cancer patients is usually completely devoid of any data as to the possible cause of the cancer present The following measures are recommended for insti

tuting an effective cancer prevention program

(1) An educational campaign about the nature of known and suspected cancerigenic agents and suggested precautionary measures among members of the medical profession public health agencies industrial hygiene organizations industrial management and labor organizations such a campaign is most effectively conducted through articles published in professional magazines trade journals organizational publications (house journals publications of manufacturers associations and unions)

(2) The past of every cancer patient should be studied for evidence of previous exposure to cancerigenic agents by obtaining a complete occupational history as well as adequate data on hobbies habits dietary deficiences endocrine imbalances parasitic infections prolonged use of certain medicinal chemicals (benzol arsenic tar aromatic medicinals estrogens androgens) administration of x rays or radium residence in regions with natural or industrial pollution of air water or soil with cancerigenic agents Such inquiries are especially pertinent for all cancer cases occurring among workers in industries with known or suspected cancer hazards

The following occupational and nonoccupational groups deserve in this respect special attention and are suggested for specially careful analysis

a Exposure to benzol and its derivatives naphthol aromatic amines toluol xylol (with possible relation to leukemia lymphosarcoma and myeloma)

Airplane dope workers
Airplane hangar employees
Alcohol (denatured) workers
Aniline workers
Art glass workers
Asbestos products impregnators
Battery (dry) makers
Beauty parlor operators
Belt scourers
Benzol purifiers
Benzol workers
Brake lining makers
Bronzers
Burnishers
Can (rubber gasket) manufacturers
Can (rubber gasket) sealers
Carbolic acid makers
Chemists
Chlorodiphenyl makers
Clutch disk impregnators
Coal tar still cleaners
Coal tar workers
Cobb ers
Color makers
Coke oven tar workers
Compositors
Degreasers
Disinfectant makers
Dry cleaners
Dye makers
Dyers
Electroplaters
Electroplate cast scrubbers
Enamelers
Enamel makers
Engravers
Explosive makers
Feather workers
Fertilizer makers
Flavoring extract makers
Galvanizers
Gashouse workers
Gasoline blenders
Gilders
Gluemakers
Inkmakers
Lacquerers
Lacquer makers
Leather makers (artificial and patent)
Linoleum workers
Lithographers
Metal washers
Millinery workers
Mirror silverers
Mordanters
Nitrobenzol makers
Nitrocellulose workers
Oil extractors
Paint remover manufacturers
Painters
Paraffin makers
Pencil makers
Perfume makers
Petroleum distillery and refinery workers
Pharmaceutical workers
Phenol makers
Photoengravers

Photographic chemical makers
Picric acid makers
Plastic textile makers
Polish makers
Polishers

Shade cloth workers
Shellackers
Shellacmakers
Shoe finishers
Shoe factory workers

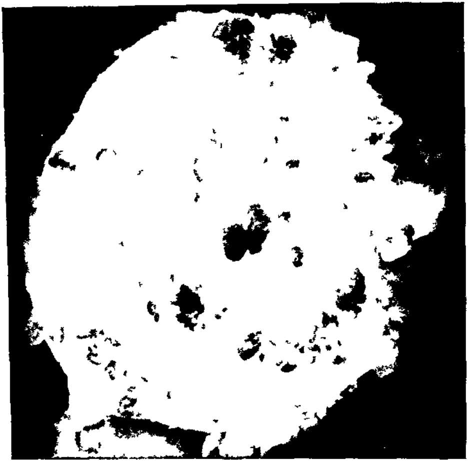


Fig 1 3 Carcinosis of the bladder in a dog following betanaphthylamine feeding

Pottery decorators
Printers
Putty makers
Pyroxylin plastic workers
Rotogravure workers
Rubber buffers
Rubber cementers
Rubber cement mixers
Rubber compounders
Rubber dippers
Rubber driers
Rubberized asbestos board makers
Rubber mixers
Rubber pressroom workers
Rubber reclaimers
Rubber tire builders
Rubber treaders
Rubber workers

Shoe heel (wood) coverers
Smokeless powder makers
Soapmakers
Tar distillery workers
Tar pitch oil etc tank cleaners
Textile fullers
Tobacco seedling treaters
Trinitrotoluol makers
Type cleaners
Varnishers
Varnishmakers
Varnish remover manufacturers
War gas makers
Waterproof fabric makers
Waxmakers
Welders
Wire insulators
Window shade makers

b. Exposure to aromatic amines, aniline, [illegible] and related aromatic chemicals (with [illegible] relation to cancers of the bladder, [illegible] and kidney) (Figure 1.3.)

(1) *Occupational exposure*

Agricultural laborers
[illegible] makers
Candlemakers
[illegible] (colored) makers
[illegible] manufactures (colored lipstick, powder, [illegible] cream, eyebrow pencil, skin tan lotions)
[illegible] dyers
[illegible] packers, mixers
[illegible] (aniline, naphthylamine, benzidine, [illegible] toluidine, etc.)
Fur dyers and workers
Gardeners (aromatic pesticides)
Inkmakers
Leather dyers and workers
Lithographers
Margarine (colored) makers
Marmalade and jelly (colored) makers
Ore flotation workers (beta naphthylamine, cresylic acid, 4 aminodiphenyl, etc.)
Painters
Paintmakers
Paper dyers and manufacturers
Pharmaceutical workers
Photographers
Photographic chemical workers
Printers
Rubber workers (antioxidants, beta naphthylamine, phenyl beta naphthylamine, butyl beta naphthylamine, etc.)
Shoe manufacturers
Soft drink (colored) manufacturers
Textile dyers
Textile printers
Wax pencil makers

(2) *Nonoccupational exposure*

Consumers of colored foodstuffs
Users of colored cosmetics
Users of dyed textiles and leather goods that bleed excess dye when coming in contact with sweat and sebum
Users (frequent) of medical preparations containing aromatic amino groups: antihistamines—allergies, hayfever, etc.; analgesics—headache, neuralgia, dysmenorrhea, arthritis, migraine; medicines (liquids, tablets, capsules, ointments) colored with aniline dyes

c. Exposure to tar, pitch, oil, soot, asphalt, creosote, carbon blacks, paraffin, anthracene (with possible relation to cancers of the skin, lung, and bladder, and leukemia)

Artificial stone makers
Asbestos goods workers
Asphalt workers
Anthracene manufacturers
Battery (dry) workers
Bricklayers
Brickyard workers
Briquet makers
Brushmakers
Cable makers and layers
Carbon black makers and users
Chimney sweepers
Coal carbonization workers
Coal tar still cleaners
Coal tar workers
Coke-oven workers
Cordage factory workers
Corkstone makers and carpenters
Cotton spinners
Creosoting plant workers
Diesel engine attendants
Electrical equipment manufacturers
Electrode makers and users
Engineers
Foundry workers
Fishermen
Flue cleaners
Fuel oil suppliers, truck drivers
Furnace workers
Gashouse workers
Gas (illuminating) workers
Generator stokers
Grease monkeys
Grease pit workers
Inkmakers
Insulators
Lamp black makers and users
Machinists
Mechanics
Metal workers
Oilers
Oil refinery workers
Oil well workers
Optical lens grinders

Ore flotation plant workers
Paint sprayers
Paraffin distillery workers
Paraffin plant workers
Pavers
Pharmaceutical workers
Pitch workers
Plastic cement workers
Printers
Road repairers
Roofers
Roofing paper workers
Ropemakers
Rubber workers
Sanitary pipe makers
Shipyard workers
Soapmakers
Shale oil workers
Stokers
Tank cleaners
Tar painters
Tar paint manufacturers
Tar workers
Textile workers
Waterproofers
Waterproof paper makers
Wood picklers
Wood preservers
Railroad workers

d Exposure to chromium and chromium compounds (chromium metal dust chromates chromium pigments chromic acid chromium carbonyl) (with possible relation to cancer of the lung and nasal sinuses)

(1) *Occupational exposure*

Abrasive makers
Abrasive workers and polishers
Asphalt refinery workers
Battery (dry) makers
Bleachers
Blueprint makers
Candle (colored) makers
Coal tar workers
Chromate chromium pigments chromic acid leather tanning compound manufacturers
Chromium ore miners and miners of other metal ores with chromium admixtures (cobalt)
Crayon and pencil (colored) makers
Dock workers unloading chromite ore
Dyestuff makers
Electroplaters
Electrolytical chromium metal manufacturers
Enamelers
Enamel makers
Explosive manufacturers
Furniture polishers
Glass and pottery frosters
Inkmakers
Linoleum workers
Lithographers
Match factory workers
Mordanters
Paint manufacturers
Painters
Paper dyers
Papermakers
Paper money makers
Paper waterproofers
Photoengravers
Photographic workers
Photogravure workers
Pottery glaze makers
Pottery makers
Printers
Refractory brick makers and masons
Rubber vulcanizers
Soapmakers
Stainless steel workers
Tannery workers
Textile dyers
Textile printers
Textile waterproofers
Wax ornament workers
Welders
Wood stainers

(2) *Nonoccupational exposure*

Persons living or working in fume and dust zone of chromate plants

e Exposure to nickel and nickel compounds (nickel metal dust nickel carbonyl vapors nickel oxide nickel sulfide nickel alloys) (with possible relation to cancer of the lung and nasal sinuses)

Abrasive manufacturers
Ceramic glazers
Chemical workers in operations using nickel catalysts
Coinmakers
Electroplaters

Enamelers
Enamel makers
German silver manufacturers
German silver smiths
Hydrogen manufacturers
Monel metal makers
Nickel alloy makers (copper, silver aluminum)
Nickel chrome alloy manufacturers
Nickel chrome wire manufacturers
Nickel extractors
Nickel ore miners
Nickel ore smelter and refinery workers
Nickel polishers
Nickel steel workers
Oil refinery workers
Storage battery manufacturers
Talc manufacturers

f Exposure to arsenic and arsenicals (arsenic metal arsenious oxide calcium arsenate sodium arsenate lead arsenate cupric acetoarsenite Paris green London purple Scheele s green Schweinfurt green Wolman salts realgar orpiment Fowler s solution Donovan s pills arsphenamine cacodylates Lewisite Asiatic pills etc) (with possible relation to cancer of skin lung bladder liver)

(1) *Occupational exposure*

Arsenic roasters
Artificial flower makers
Book binders
Bronze workers
Cannery workers peeling fruit treated with insecticides
Citrus fruit orchard workers
Cotton plantation workers
Cut glass workers
Dyers
Dyestuff makers
Electroplaters
Enamelers
Farmers
Felt hat carroters
Ferro silicon workers
Fur handlers and preparers
Galvanizers
Gardeners
Glass mixers
Glass workers
Glue manufacturers
Gold refiners
Ink manufacturers
Insecticide manufacturers
Insecticide sprayers and dusters
Japan makers
Jewelers
Lead factory workers
Lead shot makers
Linoleum color workers
Lithographers
Miners of arsenic, copper zinc silver lead ores
Oilcloth manufacturers
Oil refinery workers
Paper (colored) makers
Paper glazers
Paperhangers
Paper printers
Pelt and hair factory workers
Pencil makers (colored)
Pharmaceutical workers
Photographers
Poison bait makers
Pottery decorators
Pottery plant glaze dippers and mixers
Pyrites burners
Rotogravure workers
Rubber compounders
Rubber mordant mixers
Rubber pressors
Rubber tire workers
Sealing wax makers
Seamstresses handling fabric dyed or treated with arsenicals
Sheep dip manufacturers
Smelters of arsenic copper zinc silver lead ores
Sulfur burners
Sulfuric acid workers
Tannery workers (carriers)
Taxidermists
Textile printers
Tinners
Velvet makers
Vinery workers
Vineyard workers
War gas manufacturers
Wax ornament workers
Weavers using yarn dyed with use of arsenicals
Weed killer manufacturers
Wire drawers

Wood preserve makers
Wood preservers
Zinc mixers
Zinc smelter chargers

(2) *Nonoccupational exposure*

Users of arsenic containing drinking water (especially near arsenic ore smelters and mines) of foodstuffs tobacco and liquor contaminated with arsenicals

Users of arsenic containing medicines (arsphenamines cacodylates Fowler s solution Asiatic pills Donovan s solution arsenious oxide in tonics antiseptics antipsoriasis or caustic ointments antispasmodics) cosmetics (hair lotions)

Persons exposed to inhalation of arsenical dust spread from arsenic ore smelters or by dusting arsenicals from airplanes

g Exposure to asbestos (silicates containing calcium magnesium iron nickel and copper) (with possible relation to cancer of the lung)

Artificial wood manufacturers
Asbestos construction material workers (mill board wallboard shingle tile mortar clinker)
Asbestos insulation workers
Asbestos mill workers (crushers fiberizers molders carders)
Asbestos miners
Asbestos spinners
Asbestos textile workers (cloth blanket curtain sheets ropes cords twine thread)
Asbestos weavers
Brake lining manufacturers
Brake lining workers
Carpenters
Dye workers (acid and fireproof)
Electric wire manufacturers
Filter material manufacturers
Gasket makers
Insulation workers (pipes boilers)
Plumbers
Pump-packing mechanics
Roofers
Rubber production workers

h Exposure to solar radiation and ultraviolet radiation (with possible relation to cancer of the skin) (Figure 1-4)

Agricultural laborers
Boatmen
Cattlemen
Construction workers
Cowboys
Drivers
Farmers
Fishermen
Gardeners
Herders
House painters
Lumbermen
Miners working in surface mines
Nurserymen
Oilfield workers
Oil operators
Pharmaceutical manufacturers of vitamin D
Railroad engineers
Railroad workers
Ranchers
Road workers
Rural mail carriers
Sailors
Sportsmen
Stockmen
Sunbathers
Vine growers
Welders

i Exposure to roentgen rays and radioactive chemicals (with possible relation to cancer of the skin lung bone and liver and leukemia)

(1) *Occupational exposure*

Atomic energy plant workers
Biologists
Chemists
Gas mantle manufacturers
Laboratory technicians and attendants
Luminous dial painters handlers and shippers metal scrap handlers
Nurses
Pharmaceutical workers using radioactive isotopes and making radioactive tracer substances
Physicists
Radioactive electrostatic eliminator manufacturers and operators of such devices in textile and paper plants
Radiologic technicians
Radiologists
Radium laboratory workers

Radium refinery workers
Research workers handling radioactive isotopes and tracer substances
Roentgen and radium technicians
Roentgen mechanics

Fig 1-4 Cancer of the orbit in a rat after ultraviolet radiation

Roentgen tube manufacturers
Roentgenologists (medical electric industry aviation metallurgic chemical textile art and jewelry shoe sales beauty parlors research)
Shoe salesmen in stores using fluoroscopes for fitting
Uranium dyemakers
Uranium glassmakers
Uranium glazemakers (tile)
Uranium miners and miners of radioactive ores (pitchblende carnotite etc)
Uranium paint makers

(2) *Nonoccupational exposure*

Customers of shoe stores using fluoroscopes
Patients consuming radioactive water for medicinal purposes over long periods
Patients receiving large doses of ionizing radiation for medicinal purposes
People living in regions with radioactive ores and drinking or bathing in water of radioactive springs or residing in the waste disposal area of radioactive operations

(3) The most effective method of preventing the occurrence of cancers caused by environmental or occupational cancerigens is the cessation or arrest of any further production of all known cancerigenic agents This radical step is practical in only a few instances and is a task that concerns mainly technologists Thus benzol which formerly was used in many operations has now been replaced by less hazardous solvents such as benzine xylol toluol and petroleum ether In recent years both the German and English dye manufacturers discontinued the manufacture of beta naphthylamine after attempts to control the bladder cancer hazard associated with the production of this chemical had failed In the Swiss dye industry this goal is sought by sulfonating nitronaphthalene before this chemical is aminized and thereby producing a noncarcinogenic compound Such contaminations of alpha naphthylamine and various derivatives used as antioxidants in the

rubber industry have given rise to bladder cancer among workers handling such products

(4) Cancer prevention can be effected only by eliminating or greatly reducing contact with the cancerigens This procedure requires the installation of closed methods of production secondary conversion into noncancerigenic substances or destruction of cancerigenic components contained *in industrial and con* sumer goods by proper procedures and safe disposal of all cancerigenic wastes that might pollute the air water soil or other parts of the human environment As examples of this approach one may cite the introduction of a closed system of production in the manu facture of benzidine and to a large extent also of beta naphthylamine in some American establishments manufacturing dye and rubber antioxidants

Following the demonstration of an excessive incidence of lung cancer among the workers in American chromate plants new plants with greatly improved production methods as far as contact of the workers with chromite and chromate dust is concerned are being con structed Again it is uncertain whether such new technical advances may eliminate entirely an effective exposure to the cancerigenic chemicals because similar developments in the German chromate industry were not com pletely successful in this respect

After the discovery of carcinogenic proper ties of bunker C fuel oil the residual product of the catalytic cracking of processed petro leum oils that is used for ship and industrial fuel and in the manufacture of carbon blacks and wall board the American oil companies have undertaken a comprehensive epidem iologic and experimental technical and bio logic study of this problem One leading oil company has issued an educational booklet describing the nature of the potential hazard connected with the exposure of its workers to *this oil and has painted with a distinctive* color all pipes tanks pumps and other equipment containing this oil in its refineries In addition it requires the observation of special precautionary measures during main tenance and repair work testing loading and other manipulations of the oil For the protection of the consumer this particular company merchandises the potentially carcino genic oil only in blended form by diluting it at a ratio of 1 10 with noncarcinogenic oil

(5) Suppression of parasitic infections by suitable sanitary and therapeutic measures and proper quantitative and qualitative adjust ments of dietary imbalances when instituted sufficiently early are effective means of com bating parasitic cancers and dietary cancers *respectively*

(6) Workers to be employed in canceri genic occupations where they are exposed to agents should have a thorough medical pre placement examination Workers with previ ous exposure to cancerigenic agents in their occupational history should be excluded from further employment in such operations if such work would bring about an aggravation of their liability to develop occupational can cer Likewise they should be studied for the presence of precancerous conditions of known or unknown origin that might be activated into cancerous development by further contact with cancerigenic agents

(7) All workers employed in or entering cancerigenic operations at regular or irregular intervals should have periodic medical exami nations

(8) All workers who have once developed industrial cancer should remain under constant medical surveillance

(9) Prophylactic measures are indicated for a number of precancerous conditions of largely unknown origin such as senile kera toses cutaneous horns leukoplakia of tongue and oral cavity kraurosis vulvae kraurosis penis phimosis undescended testis erythro plasia Bowen s dyskeratosis seborrheic kera tosis intestinal polyps chronic cervicitis papillary adenoma of milk ducts and chronic cystic mastitis Moles subject to frequent trauma and irritation should be excised ex tensive third degree burns should be covered with full thickness skin grafts to reduce the *possibility* of burn scar cancers

(10) Medicinal agents with known or sus pected carcinogenic properties should be used with discrimination and proper supervision The use of ionizing radiation in the treatment of noncancerous lesions such as chronic dermatitis tuberculous *arthritis chronic ton* sillitis hyperplasia of adenoids aero otitis hypertrichosis and other disorders mainly of

cosmetic character should be discouraged, since doses are not infrequently used that may cause permanent tissue damage resulting in cancerous sequelae

Likewise the indiscriminate and prolonged administration of arsenicals tar preparations shale oil derivatives and impure mineral oil products in dermatology is distinctly inadvisable for the same reason Special caution should be observed whenever estrogenic preparations are given in large doses and over a long time to female as well as male patients since there exists some evidence suggesting that such chemicals might elicit or stimulate the development of cancer of the breast and endometrium

Because of a possible activating effect of pregnancy upon the growth of mammary cancer *pregnancy should be interrupted or pre*vented from occurring in women who suffer from breast cancer or who have undergone apparently successful treatment for this condition

Research Aspects

Inasmuch as almost all known or suspected cancerigenic agents are of exogenous origin it is probable that there exist other so far undiscovered environmental cancerigens and that the total number of cancers of environmental genesis is appreciably larger than appears from the available data The existing differences in the regional total cancer death rates *in the regional occurrence of cancers of* various sites (skin lung stomach) and their distribution between the two sexes *provide* a distinct indication for a critical study of the possible causes of such variations and of the composition of the local environmental cancerigenic patterns that may be responsible for such differences

V IMPORTANT COMPLICATIONS OF CANCER

Etiologic Factors

Most of the important *complications of* cancer are normal and thus unavoidable results of the disease and their control therefore is mainly a matter of proper therapeutic management There exists however a small number of serious complications that have been associated with certain therapeutic procedures used The administration of x rays or radium, for instance has been followed in some cases after a latent period of many years by the development of cancers in the irradiated tissues, such as skin and bones and possibly breast and uterus The therapeutic use of benzol ionizing radiation (x rays radioactive substances and isotopes) and urethane has caused occasionally fatal agranulocytosis and aplastic anemia Extensive or excessive surgical removal of axillary tissue in connection with radical *mastectomy has* been followed by the development of elephantiasis of the corresponding *arm and thereby*, partial disablement

VI DIAGNOSTIC SCREENING PROCEDURES AND TESTS

During recent years numerous technics and tests intended for screening large population groups have been devised with the purpose of discovering cancers during *their early* localized and asymptomatic stage The various *methods employed fall into two groups* periodic medical examinations of normal in*dividuals and of individuals* with suspicious symptoms and diagnostic tests for cancer performed on urine blood or other biologic material obtained from apparently normal individuals

Periodic Medical Examinations

A considerable number of Cancer Detection Clinics have been established in an attempt to improve cancer control It appears that periodic mass screening for cancers of certain accessible sites (skin lip mouth tongue larynx rectum, prostate breast uterus blood forming organs) may prove to be practicable from the standpoint of existing medical knowledge and personnel and of available *financial* resources Such schemes however are considered premature and *impractical* for the discovery of cancers of other organs and tissues particularly the lung stomach and intestine

As long as diagnostic screening procedures depend upon the voluntary co-operation of the general public it is essential that interest in cancer hazards and cancer be stimulated *and*

maintained by a skillfully conducted publicity campaign

Presumptive Cancer Tests

An acceptable diagnostic cancer test that can be used in mass screening for the discovery of early localized cancer must be efficient and reliable to a high degree must not give too many false positive results and must be simple and relatively cheap None of the numerous tests so far proposed fulfills these requirements

VII CRITERIA FOR MEASURING EFFECTIVENESS OF PREVENTIVE MEASURES

It is essential to determine the relative effectiveness of any and all preventive and prophylactic measures taken so as to be able properly to balance and adjust efforts and expenses in relation to results obtained

The only approach by which to judge approximately the effectiveness of preventive measures is offered by an evaluation of the following criteria made some 10 to 20 years after the institution of the measures

1 Morbidity and mortality rates of cancer as to total number and specific sites
2 Length of latent period
3 Sex ratio
4 Cancer multiplicity

Preventive measures that result in an appreciable reduction of the degree and duration of exposure to carcinogenic agents produce

1 A decrease in the absolute and relative frequency of cancers this effect as a rule is limited to cancers of a particular site or sites determined by the nature of the carcinogen and the type of exposure
2 A lengthening of the latent period which results in a shift of the mean manifestation age into an older age group
3 A shift in the sex ratio of the individuals affected by a particular cancer if the causative cancer hazard affects mainly members of one sex
4 A reduction in the relative frequency of multiple cancers of synchronous or metachronous appearance and systemic or nonsystemic location

The prevention of cancer by the various methods outlined can only to a limited degree be effective in the present state of our knowledge It is a valuable approach to cancer control and one that should be used to a much higher degree than has been done in the past Cancer prevention is a part of the cancer problem that belongs primarily in the domain of the practicing physician and medical epidemiologist and to which the animal experimentalist can make only secondary contributions

CHAPTER 2

The Organization of a Tumor Clinic in a General Hospital

Charles F Branch

Although this chapter is based on extensive practical experience augmented by comprehensive research and personal investigation of the many facets of this complex problem the author claims little originality for the basic concepts involved A glance at the bibliography will show that through the natural process of evolution over the past three decades many individuals have contributed various fascicles of organization and procedure until at long last there has evolved a plan of attack which in the field of cancer control is the essence of simplicity clarity and effectiveness

Not the least of these contributors was Bowman C Crowell Associate Director of the American College of Surgeons and Director of its Department of Clinical Research for twenty three years His was the task not only of establishing the pattern of standards and initiating a nationwide program of inspection and approval of cancer facilities but also his was the seemingly insurmountable and often thankless chore of stimulating many diversified groups of different economic cultural and scientific mores frequently geographically isolated to institute some type of organized cancer service or facility in their communities The growth of these clinics noted elsewhere in this chapter attests his success This accomplishment was further recognized by the American Cancer Society when in 1949 he was honored by being the first recipient of their National Award in recognition of his outstanding contribution to the control of cancer

Cancer is a major health problem that must be met intelligently realistically and aggressively by the trustees administrative officers and staffs of the large hospitals in this country The consensus of authoritative contemporary opinion in the field of cancer control is that further expansion of group effort in cancer services in general hospitals together with continuous professional and lay education constitutes the only immediate means of reducing cancer morbidity and mortality Experience conclusively proves that improved service for the cancer patient through earlier diagnosis prompt and adequate treatment and a greater distribution of available cancer facilities must precede any substantial progress in cancer control

In considering the organization of a tumor clinic in a general hospital one can scarcely do better than to review the growth and development of such facilities since the original fervent appeal of Ewing Greenough and Gerster in 1929

In 1930 the American College of Surgeons with the approval and at the request of th American Society for the Control of Cancer (now the American Cancer Society) formulated a minimum standard for cancer clinics in general hospitals In October 1933 after inspection and careful consideration of the installations then in operation the Board of Regents of the College published a list of 158 approved facilities In 1950 the Public Health Service in its excellent Publication No 14 Cancer Services and Facilities in the United States [27] listed 613 cancer clinics and 165 diagnostic clinics or tumor boards as well as 14 recognized hospitals devoted exclusively to the care and treatment of cancer patients Under the recently reorganized Cancer Com

mittee of the College of Surgeons and the current standards for approval expressed in their brochure Manual for Registries and Cancer Clinic Activities [10] the Board of Regents in October 1956 published a list of 713 approved cancer programs in the United States its territories Canada and Cuba This list also includes the cancer hospitals above noted

The number of cancer detection centers operating in this country varies with the authority quoted and the complexities of that philosophy are considered in another chapter of this publication We have long been of the persuasion that cancer detection begins in the doctor s office Professional education directed along these lines should take the form of refresher courses, graduate medical assemblies or even mail order home study courses directed from some approved medical agency such as a regional medical school Most of us would admit that the three years of intensive pilot experiment and the expenditure by the American Cancer Society of millions of dollars and man hours for lay and professional education along these lines have at least resulted in focusing attention on the theorem that the family physician is the key man in cancer control Furthermore this extensive lay education has been most productive in stimulating the average person to seek medical advice much earlier than usual thus enabling physicians to detect sooner than otherwise the early cancer precancerous lesions areas of chronic irritation or abnormal physiologic conditions that might lead to cancer—as well as to discover the early manifestations of many other diseases

Time and space preclude the consideration here of other forms of approved cancer services In passing it should be noted that all that is written about the organization of a cancer clinic (Cancer Consultation and Treatment Service) applies with equal logic and force to cancer diagnostic clinics (Cancer Consultation Service) or as designated in some sections of the country Tumor Board The fundamental difference between the two concepts rests entirely on whether or not the modalities of treatment such as surgery x ray radium the radioactive isotopes and chemotherapeutic materials are *available* We presume to use these archaic terms because general medical semantics and common usage have firmly fixed them in the vocabulary of the average physician throughout the land On the other hand we would be woefully negligent if we failed to emphasize the changing trend in terminology expressed in the title of the Cancer Committee s brochure [10] and again note that the Board of Regents now issues its report of Cancer Programs Approved without any further definition of terms Not everyone would agree on a categorical classification of cancer facilities but for the time being we would recommend strict adherence to the type of such facilities now recognized jointly by the American College of Surgeons the American Cancer Society and the Public Health Service and as explicitly approved by the Joint Commission on Accreditation of Hospitals The pattern here presented has stood the test of time trial and no inconsiderable tribulation It would be absurd to presume that it will fit the need of every city town and hamlet or that in some instances and with the most altruistic motivation it will do more than augment certain local rancor and righteous feelings of prerogative On the whole however, *it is sound* and from its many suggestions any community or group of serious minded physicians can find or evolve a plan to fit their particular needs circumstances and pocket book The organization of such facilities within a general hospital must of necessity vary considerably depending on circumstances of personnel equipment physical plant and the association of the clinic with academic programs and voluntary health agencies The constant factor that *must* be present if the blessing of the approving authority is sought is the absolute insistence that any cancer program shall have and maintain an active Cancer Registry Scores of approved cancer clinics had their genesis in small enthusiastic groups of individuals who at first were compelled by some modification of the circumstances noted to operate as a diagnostic clinic Some actually had their inception in extramural space associated with neither a hospital or medical school As they grew the need became more apparent enthusiasm and public support increased Needed equipment

and personnel frequently became available often through the interest and co operation of the local chapter of the American Cancer Society or other public spirited agency and overnight these organizations became fully equipped and operating cancer clinics with all the vital attributes of such treatment centers

Cancer is the second most common cause of death in this country, taking a toll of over two hundred thousand lives annually Even with insufficient statistical control (cancer is a reportable disease in only twenty eight states) reputedly nearly one million other persons are afflicted with the disease at all times It is no scarehead when the Public Health Service points out that because of our increasing longevity 20 per cent of the boys and 22 per cent of the girls born must look forward to suffering from this disease at some time in their lives In spite of our close contact with the field the best available records we could gather at the College of Surgeons in 1950 indicated only slightly over five hundred thousand annual visits to cancer clinics throughout the country These awesome facts substantiate the reassuring attitude of the American Cancer Society and the Division of Cancer Control of the Public Health Service in their forthright and generous support of the American College of Surgeons in its aim to secure the eventual distribution of cancer clinics throughout the country in such numbers and in such strategic locations as to make their service available to the greatest possible number of patients

What constitutes an adequate number of cancer clinics is a moot question As Pack has so succinctly put it "The number of cancer clinics in any community depends largely on local needs and existing hospital facilities This is a problem which cannot be solved by rule of thumb or gross population There can never be too many diagnostic tumor clinics in any city but for cancer therapy it is more ideal and less expensive to have properly located treatment centers with adequate x ray and radium facilities Assuming that for many reasons it is impracticable to have a cancer clinic in a general hospital of fewer than one hundred beds and frankly admitting that not all large hospitals need such installations in the light of the supposed incidence of the disease twenty years ago it was originally postulated there should be a cancer clinic available for each 200,000 of the population This figure has been approximated In fact, several states have long since exceeded their theoretical quota Within the past few years and in the light of the ever increasing incidence of cancer, many authorities now believe we should plan a cancer clinic for each 100 000 of the population To some this arbitrary establishment of a didactic figure is too much a rule of thumb and serves no useful purpose However, considering the latest figure of 713 approved cancer programs against these potentialities and the existing approved hospital facilities it appears that at the moment there are approximately 620 approved general hospitals of between 100 and 200 beds and 336 approved hospitals of over 200 beds which have no cancer clinics In other words there are an estimated 956 approved hospitals in this country that could accommodate a cancer program of some type an increment that would provide our potential cancer patients with a theoretically adequate number of facilities

The formation of a tumor clinic in a general hospital is not a difficult task Assuming the hearty support of the staff and administration certain material advantages and economies in the utilization of personnel equipment and space immediately become apparent Such a liaison provides the cancer patient and the community with the best possible method of handling the various perplexing and distressing aspects of this disease In considering definitive action relative to the organization of such a clinic in a general hospital, no better critique of the value and stability of such facilities can be offered than to suggest that the reader compare the advice offered in a paper by Pack in 1934 and the *modus operandi* recommended by the American College of Surgeons in its publications Our brochure of 1947 [15] completely outlined these procedures and although the patterns can be overlaid with scarcely a hiatus one should follow the latest edict and suggestions of the Cancer Committee [10] in establishing any type of cancer program at this

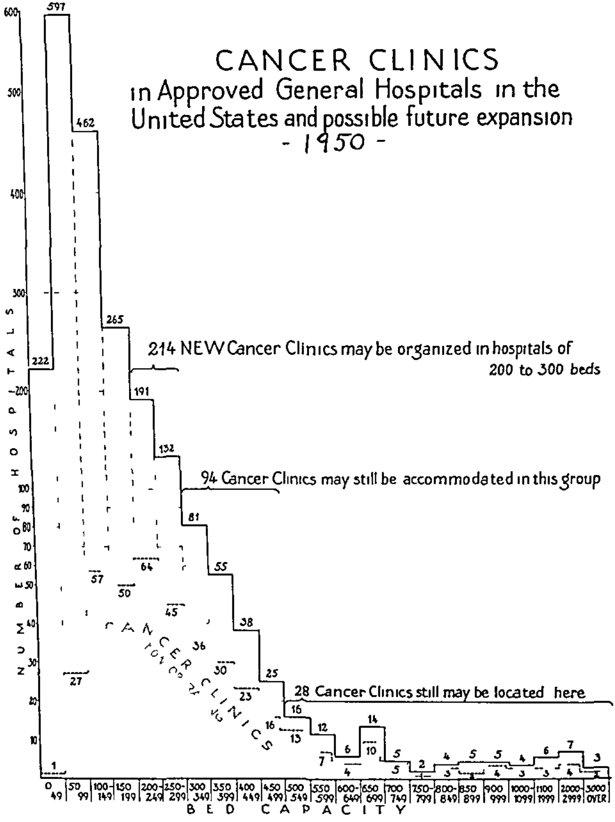


Fig 2 1 (Courtesy American College of Surgeons)

Minimum Requirements for Approval of a Cancer Registry and Cancer Clinical Activities

Cancer activity must be conducted either in and by the staff of a hospital approved by the Joint Commission on Accreditation of Hospitals or in lieu of this by an organization the cancer activities of which has the formal approval of the local county medical society

I COMMITTEE ON CANCER

There shall be a Committee on Cancer of the hospital medical staff consisting of physicians directly concerned with the diagnosis and treatment of cancer that shall be appointed by the appointing authority of the medical staff The duties of this Committee shall be to initiate supervise and appraise the cancer program and to report to the medical staff at least annually It shall maintain close liaison with the Tissue Committee

II CANCER REGISTRY

It shall be a requirement (after December 31 1955) for approval that a properly functioning cancer registry be in operation which records every patient private and public inpatient and outpatient, upon whom the diagnosis of cancer is established This may be the only formal cancer activity conducted

Each year a report will be made to the medical staff of the current work of the registry including five year end results as they become available through continuing follow up

III CANCER CLINICAL ACTIVITIES*

With the Cancer Registry as a requirement the program may offer (a) a Cancer Consultation Service or (b) a Cancer Consultation and Treatment Service

A CANCER CONSULTATION SERVICE

1 Organization

There shall be a definite organization of the Service with representation from the various departments of the hospital concerned with the diagnosis of cancer

2 Patients

Reference to the Cancer Consultation Service of all patients in whom the diagnosis of cancer is to be considered shall be either voluntary or obligatory preferably obligatory in at least the case of public patients in accordance with the recorded vote of the medical staff and the governing board of the hospital

3 Equipment

In addition to the usual diagnostic equipment required in every approved general hospital there shall be such other diagnostic equipment as is necessary for the diagnosis of cancer

4 Clinical Record

The clinical record shall be a complete chronological account of the cancer patient s course including laboratory diagnoses and an autopsy diagnosis when available

5 Treatment

No treatment is offered by the Cancer Consultation Service

6 Clinical Sessions

Regularly scheduled clinical sessions shall be held as often as necessary for proper service to the patient preferably at least weekly

B CANCER CONSULTATION AND TREATMENT SERVICE

1 Organization

There shall be a definite organization of the Service with representation from the various departments of the hospital concerned with the diagnosis and treatment of cancer

2 Patients

Reference to the Cancer Consultation and Treatment Service of all patients in whom the diagnosis and treatment of cancer is to be considered shall be either voluntary or obligatory preferably obligatory in the case of public patients in accordance with the recorded vote of the medical staff and the governing board of the hospital

3 Equipment

In addition to the usual diagnostic and therapeutic equipment required in every approved general hospital there shall be such other diagnostic and therapeutic equipment as is necessary for the diagnosis and treatment of cancer

4 Clinical Record

The clinical record shall be a complete chronological account of the cancer patient s course including laboratory diagnoses and an autopsy diagnosis when available

5 Treatment

The treatment of cancer patients shall be entrusted to the members of the hospital medical staff except in cases where adequate treatment must be procured elsewhere in keeping with the collective recommendations of the group

6 Clinical Sessions

Regularly scheduled clinical sessions shall be held as often as necessary for proper care of the patient preferably at least weekly

*Because of the wide variation of operational patterns descriptive organizational terminology may vary as tradition and local conditions dictate For example certain groups may wish to use the terms "tumor board" "neoplastic clinic" "cancer clinic" "cancer service" et cetera.

Fig 2 2 (Courtesy American College of Surgeons)

time Although other organizations and individuals have prepared outlines of procedure and format it would be trite indeed to try to improve on the material prepared by the American College of Surgeons the American Cancer Society or the Public Health Service for the guidance of those interested in establishing tumor clinics in their respective hospitals Such outlines and advice born of years of experience are generously provided by these organizations to any properly authorized person who may request them Careful scrutiny of all available literature provides no more concise information than that depicted in Figures 2 2 and 2 3

The organization of a cancer clinic in a general hospital must of necessity vary considerably depending on circumstances dictated by available staff ancillary personnel equipment teaching affiliations hospital facilities and funds as well as on the size of the community to be served and the association of this projected organization with other voluntary health and welfare agencies (In New York State the Department of Health recognizes the value of co ordinating effort with at least eight different agencies) In years gone by when in our ignorance we were happily possessed of an undeveloped social consciousness such considerations as the latter would have been poorly understood and would have mattered not at all This is no longer so A close liaison with and specific knowledge of the vital role played in the field of cancer control by the American Cancer Society the Division of Cancer Control of the State Health Department and the Cancer Committee of the State Medical Society of each state the regional cancer committees of the American College of Surgeons the cancer co ordinators of our medical schools the Visiting Nurse Association and many other voluntary nonprofit health services is fully as essential as the space provided by the hospitals within which to work

In spite of this new and broader concept of the organization of a cancer clinic an imperative preliminary step is to obtain the hearty support and co operation of the medical staff of the hospital It must not be supposed that the entire staff will subscribe to Ewing s dictum that cancer is no longer a one man job For various egocentric reasons the attitude of certain members of the staff may be found to express it delicately less than enthusiastic Many authors have defined this theorem but no one has made it more clear than Pack who remarks No one physician has sufficient knowledge and experience in the diagnosis and treatment of neoplastic diseases of all organs to be independent of the opinions and aids of his medical confreres Group judgment as to diagnosis and proposed plans of treatment are preferable as they are based on the agreements of surgeon radiologist pathologist etc The patient benefits by the knowledge skill and experience of physicians who have devoted themselves to the diagnosis and treatment of this disease

A tumor clinic in a general hospital should be autonomous within the organization of that institution in the sense that it is a service as distinct and separate as any of the other hospital services Its interrelations with the other departments however of necessity are close and intimate ones Whether a case originates in the outpatient department or is referred as a private patient diagnosis assignment to service for definitive care discharge and follow up all demand the closest departmental co operation A tumor clinic is an exercise in sublimation of self for the greatest good of the patient suffering from cancer Its reward is an unrivaled opportunity for self education scientific investigation and a post graduate course in oncology Seldom does the average physician see more than a dozen cases of cancer a year It has been repeatedly demonstrated that the concentration of cancer cases in a special service insures better care of these patients through consultation between those best versed in the various methods of diagnosis and treatment as well as stimulates the keeping of accurate and uniform records and a carefully organized follow up system to detect early recurrences or metastases and the evaluation of treatment and general procedure Further it is the only means whereby accurate statistical material can be gathered on an accumulative experience so that this material may be appropriately disseminated through authoritative sources and correlated with a state cancer record registry or whence it may be utilized for clinical research or in

Organizational Plan for Cancer Programs

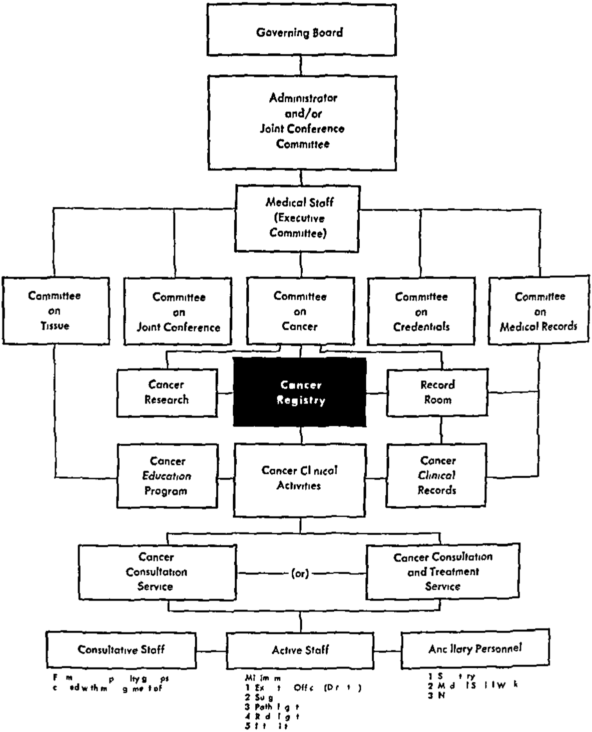


Fig 2 3 (Courtesy American College of Surgeons)

tegrated with research in the basic medical sciences

No tumor clinic is better than its personnel All important as are the medical staff and their consultants it is equally mandatory that any active cancer facility must have adequate and well trained secretarial service nurses conversant with the special problems of cancer patients social service workers clerks or interne service and some type of extramural household nursing service such as is customarily provided by the Visiting Nurse Association or by the Public Health nurses As we have noted in a previous publication [15] A cancer clinic service will attain greater efficiency when directed by a permanently designated personnel selected from the various departments for their previous training or experience in oncology or their ability in some special field as it relates to malignant disease and their willingness to devote special time and effort to this endeavor The key members of the cancer clinic staff are the pathologist radiologist general surgeon and internist Also essential is the availability of the services of representatives of the surgical specialties—gynecology urology otorhinolaryngology orthopedics as well as dermatology and such other special departments of the hospital as may be concerned with the diagnosis and treatment of cancer The services of an oral surgeon are frequently of great value It will generally be found that a rotating system of service in the staff of a cancer clinic will not produce the increased efficiency and cumulative experience provided by a permanent group In justice to the cancer patient who ideally should remain a lifelong study continuity of service is not only desirable but necessary

The selection of the director of the tumor clinic should be approached with care for about him frequently revolves the success or failure of the venture He should be an individual qualified by training experience and personal interest in the cancer problem He must be an organizer and a leader with that rare human trait a happy blending of enthusiasm and sagacity It has been our experience the country over that most successful mentors of tumor clinics are such uncontroversial and nonsuspect members of the staff as the pathologist or radiologist An interesting sidelight has been the number of dermatologists and pediatricians we have discovered in this role However it cannot be emphasized too much that the general care and treatment of cancer tends to be a surgical problem and with that in mind we have found that one of the well accepted and better trained young surgeons frequently provides the necessary spark to enlist the confidence of the staff and attract the needed community support

The fact that many hospitals are not so extensively departmentalized as to provide all the specialists suggested should in no way act as a deterrent to any ambitious group bent upon forming a cancer consultation and treatment service or a diagnostic clinic One item of personnel is imperative in establishing such an organization and that is good secretarial assistance We have frequently found that even with an adequate staff contingent the success or failure of a clinic has hinged on this one person Part time assistance donated by a volunteer worker or begrudgingly bestowed from an overworked record room may be sufficient in a small clinic seeing only a half dozen new cases each week and perhaps twice as many follow ups but such an arrangement is lethal to a large clinic Full time intelligent co operative secretarial assistance is imperative to successful operation of any active clinic Physicians on the staff who have their practice to attend to and to whom the cancer clinic is only a half day exercise once a week (and the majority of the clinics of the country so operate) must look to a thoroughly trained and competent person to hold the organization together Aside from the relatively simple task of taking notes and keeping minutes of the various clinical and formal sessions of the staff other routine duties consist of keeping the cancer registry records and files of the clinic and preserving their continuity keeping the tickler system on the follow up cases properly aligned and functioning making appointments frequently assigning and always following patients through their various phases of hospitalization and treatment and attending to the correspondence including all letters to referring physicians and social agencies That this can be usually is and should be a full

time job is sadly appreciated by no one more than those who have had to struggle to maintain a functional cancer clinic with less

Social service workers are desirable in any clinic but they are indispensable in large metropolitan installations In this era of multiple interdependent if not actually interlocking social agencies it is the worker in this field who should know her community resources of funds for the indigent and the medical facilities available for the terminal care of cancer sufferers Such workers are invaluable in tracing the lost follow up and transient patients as well as in interviewing and investigating family resources One of their most valuable areas of assistance is in co ordinating the efforts of the clinic and community in assisting terminal care patients at home In smaller communities and rural areas a dynamic clinic secretary or visiting nurse can accomplish these same ends but in large centers of population social service workers are a necessity if the cancer clinic load is to be properly distributed

Aside from bedside nursing and home nursing care of those ill with cancer in no other field of nursing endeavor is the responsibility greater than in the tumor clinic As Cameron remarks The problems created by cancer for the patient and his family are more than physical ones they involve major psychological adjustments and financial burdens which are difficult if not impossible for the family to meet alone Perhaps no other disease demands of the nurses so much sympathetic understanding of human relationships and such wise guidance in building morale to help the patient and his family meet their problem If a training school exists in the hospital student nurses should be given every opportunity to study the methodology and philosophies of the tumor clinic and to perfect themselves in the special technics associated with the bedside care of the cancer patient If the hospital is affiliated with a medical school opportunity should be provided for the cancer co ordinator of that institution to utilize the clinical sessions for undergraduate section teaching It goes without saying that residents and internes on the hospital staff should rotate through the clinic

Under no circumstances should the general staff be excluded from an interest in the cancer clinic Their attendance and participation especially at the formal conferences should be encouraged as part of the whole program It is also essential that departmental representatives on service participate in presenting and discussing cases from their respective departments and it is equally advantageous for physicians to take a similar responsibility when they refer patients to the clinic If the State or County medical society has established a panel of physicians who have been particularly contributing to the community cancer program by carrying on cancer detection or diagnostic work special effort should be made to arrange for them to follow patients discovered through their effort It should be particularly emphasized that a cancer clinic in a general hospital in no way alters or disturbs the relationship between the physician and his patient If possible the general practitioner on the staff should be represented in the cancer clinic and in this instance a rotating service might well be considered One of the greatest advantages of a tumor clinic is to provide a golden opportunity for graduate education in the special diagnostic knowledge technics equipment and various modalities of therapy not found in the office of or readily available to the average physician

Two types of conferences should be conducted by the staff of most tumor clinics—the clinical session and the formal conference At the clinical session the group is concerned with investigation and discussion of new cases observation and specialized care of patients under treatment and the follow up or rehabilitation of old cases Whether held in the outpatient department medical school clinic rooms or possibly in buildings outside the hospital it provides the common meeting ground on which the pathologist radiologist and surgeon see and discuss cancer patients from their varying viewpoints With increasing experience their comprehension of malignant disease in its many forms their skill in the diagnosis of obscure cases and their appreciation of results to be expected from the various forms of therapy become cumulative and confer upon the patient the benefits of impartial

intelligent care and follow up that can be gained in no other way These meetings should be held at intervals sufficiently frequent to take care of the case load of the individual clinic varying between daily sessions in large teaching centers to weekly or perhaps biweekly in areas where the number of patients is appreciably smaller In general it may be considered that if a clinic is so small as to warrant meeting only monthly then the case load is not sufficiently heavy to justify the maintenance of the clinic and all the necessary ancillary services Absurd as it may seem to some a word of warning should be injected relative to those unreconstructed centers of healing in which hallway or curbstone consultations are considered the essence of a cancer clinic Such tactics estimable as they may be in the general practice of medicine have no place in the function of an established and accredited cancer clinic

Just how a clinical session is conducted varies directly as the space time case load and personnel dictate In the first place too much publicity cannot be given through lay and professional channels announcing that a cancer clinic is held each ——— day at 10 00 A M in the Outpatient Department of Blank Memorial Hospital In a tumor clinic in a 300 bed general hospital meeting once a week at which time four to eighteen patients are examined as well as ten to twenty follow ups the general procedure might roughly be outlined as follows The secretary makes the necessary arrangements with the staff and nursing service to have brought to the clinic all ambulatory or reasonably mobile cancer patients in the house who were admitted through or are the responsibility of the cancer clinic Naturally their records accompany them The secretary checks her files approximately two weeks in advance and removes the working or follow up control cards flagged with suitable detachable colored markers which indicate the patients due for checkup on that particular date Postal cards or preferably short form letters are sent to perhaps thirty such persons In case there is any question about reaching them the social service worker the visiting nurse or in some instances even the police are asked to contact individuals in remote areas or without telephones to inform them of their desired presence at the tumor clinic on any given date

With the clinic in session one of two methods of procedure in examining patients is customarily followed In either instance the secretary nurse or intern in charge sees to it that patients are not kept waiting unnecessarily but are promptly assigned to cubicles or to conference as the case may be If space permits and the clinic is relatively large and active the deposition and examination of patients in cubicles is advantageous and to be recommended the clinic group proceeding from cubicle to cubicle with the recording secretary and nurse in attendance In each instance the patient is thoroughly examined if possible a diagnosis made (if not it is imperative that diagnostic procedures be recommended) and definitive treatment decided upon The secretary makes record of all this usually in a summarizing statement though if a valid minority opinion is pertinent it also should be noted In many clinics throughout the country the surgeon or a member of the examining team puts the entire procedure and a summary of opinion on the cylinder of a dictating machine immediately after examining each patient thus eliminating any confusion or possible mistakes concerning the group thinking about any given patient In smaller clinics where space and personnel are limited patients are frequently presented by the intern or staff member to the clinic group seated in round table fashion in a diagnostic area Here too each clinician is given an opportunity to examine the patient and to express his opinion Definitive suggestions are made relative to diagnosis and treatment preferably after the patient has been removed From these opinions in time are evolved the technics and policies of that clinic concerning procedure in cases of various types of cancer observed in that locality

Whether the clinic is organized as a consultation service a diagnostic service or is blessed with the full accouterments for treatment it should be in a position to offer certain immediate diagnostic procedures In this day of almost unlimited cytologic diagnosis it is becoming increasingly *de rigueur* to examine the cervical smears of all females visiting the clinic and the same technics are becoming

more frequently applied to material obtained from less accessible sites Punch or cold knife biopsies and frozen sections of questionable neoplasms in accessible areas may be carried out and thus may save the patient and the clinic workers many days of invaluable time as well as unnecessary occupancy of a vitally needed hospital bed for a protracted period of observation Also during the clinic period house cases are further studied to determine end results suggest further treatment or define home care or rehabilitation therapy The follow up cases that come in can ordinarily be handled somewhat more quickly but the purpose of their presence is negated if one approaches them in a casual slipshod manner They should be carefully studied as to their general health and psychic and economic adjustment as well as for any possible recurrence or metastases Expensive as it is radiography should never be scrimped in determining the site of any possible recurrence Useless though it may seem in a case of advanced recurrence such radiologic record will frequently be the only means of completing invaluable follow up information on patients who are bound to leave the control of the clinic and who will in all probability never come to necropsy

Following the clinic assignment of new patients through the customary admitting channels to the various house services or to x ray for therapy automatically becomes the problem of the secretarial and nursing staff of the clinic Records have to be collected annotated and refiled Future contacts have to be carefully checked on the no show follow up cases And last but no means least relatives friends and transportation agents who accompanied patients to the clinic and who may have to wait all afternoon to take them home after a course of therapy or diagnostic procedures have to be met and talked with and otherwise treated like the intelligent responsible individuals they are Not infrequently they have to be fed and sheltered particularly if the weather is inclement and the clinic is a considerable distance from available public facilities The matter of effecting good public relations or simple compassion with these frequently distraught fearful or completely bewildered individuals has been so consistently overlooked in most cancer clinics that I am constrained to add this line in their behalf

Crowell has succinctly expressed the necessity of holding formal cancer clinic conferences and their importance to the clinic staff as well as the educational opportunity afforded by such exercises [15] 'The general hospital will find it beneficial to hold full staff conferences conducted by the staff of the cancer clinic at which selected cases of cancer are presented The interval may vary from monthly to quarterly Physicians from the community and surrounding area should be regularly notified by mail of such conferences Interest may be stimulated by occasionally inviting a well known authority in some field relating to cancer to conduct a teaching clinic' Pathological specimens microscopic slides records and patients should be presented The value of such conferences is chiefly educational but it also should acquaint the practitioner with the advantages to be obtained by referring his tumor problems to a group cancer clinic Although conferences of this type are of value from several standpoints they should be a supplement to the clinical sessions before referred to and not a substitute for them

In considering what patients should be referred to the tumor clinic it is difficult to improve on the recommendations of the American College of Surgeons The goal is to make the services of cancer clinics available to as many patients as possible In time the benefit realized from the superior service offered to the tumor patient will in itself attract more and more patients Thus Pack remarks After the establishment of a tumor clinic in a community it will be observed that the delay between the onset of symptoms and the appearance of the patient in the clinic will noticably decrease year by year Early submission for diagnosis results in a higher percentage of cancer cures This increase in the relative percentage of cases classified as early or operable may be attributed to the educational activities of the clinic the awakening of public and personal interest in cancer prevention and treatment the missionary efforts of patients who have been satisfactorily treated and the co-operation of the physicians in the community

In the hospital itself, it is desirable that

every outpatient and ward patient presenting a benign or malignant tumor or precancerous condition be automatically referred to the cancer clinic for diagnosis and recommendations as to therapy The tumor clinic should receive for treatment not only the patients with advanced incurable cancers referred to it from the surgical service and other departments in the hospital but should be privileged at least to see in consultation every patient with a benign or malignant tumor But if the reference of patients to the cancer clinic is to be voluntary, at least every patient in whom a diagnosis of cancer is established should be registered in its files and referred to it for follow up Under the established rules of the new Manual for Registries and Cancer Clinic Activities [10] this procedure is now mandatory The clinic should not serve merely as a diagnostic and follow up service but should offer advice on various methods of therapy that may be employed When therapy, surgical or otherwise is to be carried out in departments the department representative on the cancer clinic staff may frequently have the case assigned to him or assist in the therapeutic procedure

The private patient should have ready access to the services of the cancer clinic staff when referred by written request of his physician or accompanied by him A considerable proportion of the patients seen in a cancer clinic should be ambulatory patients referred from physicians offices

Although one might assume that equipment and space required would differ greatly in clinics of varying size the fact remains that the general pattern is identical and that certain fundamental pieces and types of apparatus are imperative in any clinic As previously intimated the mutual advantages accruing to all from the utilization of space in an approved general hospital will effect economies of personnel and equipment unequaled by any other plan Aside from the space required for a sufficient number of separate dressing and examining rooms or cubicles waiting rooms offices or consultation rooms file space treatment rooms etc such institutions provide the necessary diagnostic operative and treatment facilities not easily found elsewhere All necessary instruments for endoscopic examination of the rectum esophagus bronchi bladder and female pelvis as well as biopsy and electrosurgical instruments must be available An old adage frequently quoted at cancer symposia to the effect that one of the greatest crimes in modern medicine is the rusting speculum buried in doctors desks is not without an unfortunate element of truth

All diagnostic facilities of the laboratory should be made available to the clinic through the pathologist in attendance and rapid smear technics and frozen sections should be resorted to if indicated

Effective treatment of cancer cases requires that the department of radiotherapy should be equipped to develop high voltage x ray therapy and that it should have at its disposal an adequate supply of radium A discussion of equipment for high voltage x ray therapy not infrequently becomes controversial and recommendations should always be sought from competent radiologic authorities Present accepted standards require therapy apparatus with a minimum peak strength of 200 kv It is also desirable that 150 to 200 mg of radium in suitable applicators be available Needles plaques an Ernst applicator and a culposcope are essential If at first the clinic lacks funds to purchase a useful amount of radium it can be rented or obtained from well recognized sources Similarly an appropriate amount of radon may be obtained when required It is reasonable to assume that the use of radioactive isotopes by any physician should be carefully monitored by the radiologic department or by a physicist if the institution affords such an individual To obtain isotopes for diagnosis or therapy the Atomic Energy Commission requires specific training and certification of the individual using such substances Chemotherapeutic substances may frequently be given patients by uninformed or untrained individuals and in the light of their profound toxicity perhaps it is logical to assume that the therapeutic use of such substances should be under the analytic eye of the division of internal medicine and the laboratory

With no idea of disturbing the organized unit record system within the hospital it is nevertheless highly desirable and now more or less mandatory that a separate filing system be provided for the case histories of cancer patients attending the clinic These should be

in the quarters occupied by the clinic or the office of the secretary of the clinic Every patient should receive a clinic number and should be cross indexed so that he may easily be located by name number yearly group diagnosis, and regional incidence of disease The minimum requirement for the approval of any cancer program now makes it mandatory that a properly functioning Cancer Registry be in operation that records every patient private and public inpatient and outpatient, upon whom the diagnosis of cancer is established In fact this may be the only formal cancer activity conducted by a hospital This Registry must contain adequate identifying and diagnostic information with a basic abstract of the clinical record and an annual follow up note for as long as the patient remains alive From this base the content may be elaborated as far as those conducting the registry desire Patients admitted directly to the hospital and seen later in the clinic should have summaries of their hospital records in the clinic file The five elements that may be considered basic for an acceptable record system for cancer clinics or cancer diagnostic clinics are (*a*) the cancer registry (*b*) clinical record (*c*) patient index (*d*) follow up control file and (*e*) diagnostic index and code

In studying the organization of cancer clinics throughout the country the most glaring deficiency has been a consistent lack of uniformity and adequacy of the records Naturally this varied according to the interest personnel teaching affiliation and economic status of the clinic involved For thirty years the American College of Surgeons has stressed the necessity of keeping adequate records in cancer clinics Yet in spite of that insistence and all that has been done to demonstrate the practical value of such records as recently as 1950 it was only with the greatest difficulty that the College through its thousands of Fellows and hundreds of associated clinics was able to collect for its files a meager forty five thousand completely authenticated and well recorded cases of five year survivals Admitting that this phenomenon does not entirely reflect the perfection of the various clinics involved it is nevertheless a sad commentary on available records in cancer clinics in general One of the most outstanding accomplishments in the annals of modern cancer recording is that of the doctors of Connecticut in conjunction with the State Department of Health ably reported by Eleanor Macdonald During our association with the work of the College it became apparent that the abstract record forms evolved by the Committee on the Treatment of Malignant Disease (now the Cancer Committee) were not generally in use and only occasionally were even being copied or used as a model by local groups In an endeavor again to emphasize the dire necessity of correcting various deficiencies in cancer clinic record systems Schaefer wrote an outline of an acceptable record system which, though not gaudy certainly is utilitarian The opening paragraph should be prominently displayed in every cancer clinic and every record room in the country

At a time when so many volunteer health agencies contribute to the support of cancer clinics and to the welfare of patients with that disease and when in so many states cancer is a reportable disease it becomes increasingly desirable and necessary that hospital records of cancer cases contain information necessary for critical analysis as to classification therapeutic measures and end results Accurate complete records are imperative in any study of etiology pathology and methods of treatment Furthermore different types of malignant disease require dissimilar emphasis on various phases of record taking Thus some special effort at standardization of records is important and is the responsibility of the staff of the cancer clinic

Recently the statisticians of the Division of Cancer Control of the National Cancer Institute using comprehensive report forms developed there ran pilot experiments in a few states where cancer is a reportable disease Although somewhat cumbersome these forms are entirely adequate and susceptible of being easily filled out by any intelligent secretarial or clerical help When returned to a State Department of Health or some central point much exhaustive information is easily transferred to punch card systems which methodology will in time produce accurate current and representative data concerning types trends and treatment of cancer in the population of the area surveyed The most recent compilation of statistical results by Dorn Cutler and their associates in Public Health Monograph No 29 *Morbidity from Cancer in*

the United States [21] is a fitting monument to the validity of this theory so long embraced by the American College of Surgeons as well as to the foresight capacity and industry of the National Cancer Institute at Bethesda When this type of procedure becomes available on a national basis then and only then will those devoting themselves to therapy and research be able to discover heretofore obscure trends and adduce other information that may prove to be of inestimable value in solving the riddles of etiology and cure

The follow up of patients is an essential duty of any modern progressive hospital or clinic and is the only method by which an adequate evaluation of therapeutic methods can be determined accurate statistics compiled *and our responsibility for the continued* welfare of the patient be completely fulfilled It is now generally accepted that every cancer patient should be periodically followed up for life It is also generally agreed that all cancer patients should be re examined at least every three months for the first year or two semi annually at least for the next year and annually thereafter For maximum efficiency in follow up there must be systematized effort which depends upon co operation between the secretary and the social service worker or the agency assisting in the field Every patient should have an appointment card on which the date of each future visit is recorded as well as in an appointment book in the clinic The chart or index card of each patient who fails to return may immediately be flagged by a suitable detachable marker and the individual notified by mail of the next date at which he may be seen For this purpose a form letter is timesaving but it should be tactfully worded reminding him of his failure to appear and impressing upon him the importance of periodic examinations Personal letters however are more effective than the usual form letters If there is no response to this reminder a home visit by a social service worker is most effective otherwise information may be obtained from private physicians relatives or friends For this purpose it is advisable to record the names of two friends as well as the nearest relative in the social data obtained at the first visit Information on "untraced cases may often be obtained from such other sources as an insurance company telephone company employer town clerk or postmaster overseers of the poor or charitable organizations veterans organizations service clubs or the police district nurse or state department of vital statistics Effectiveness of follow up is limited only by the ingenuity and perseverance of the person handling it provided adequate funds are available Many cancer clinics with a well organized system are able to follow 95 per cent or more of all cases admitted even in large cities In smaller communities the task is considerably less difficult Channing Simmons [78] in a terse but comprehensive paper points out that the chief requisite of a good follow up system is the record of

1 The Christian name of both husband and wife
2 The addresses of two friends—one of whom is a man not a relative who has a permanent address
3 The names and addresses of the employers of both the man and wife or son or daughter
4 The telephone numbers of as many of the above as have telephones
5 The name and address of the physician referring the patient
6 The name of the insurance company in which the patient s life is insured
7 (*And in this day one s Blue Cross Blue Shield number*)
8 (And the inevitable Social Security number)

We would be less than realistic if we failed to emphasize the ever increasing necessity for physicians to obtain the fullest knowledge of and maintain a cordial and forthright co-operation with the many social agencies materially affecting all phases of the cancer story in our country today One of the best considered most practical and beautifully presented efforts outlining the field of cancer control is a Manual For Public Health Officers prepared by Herman E Hilleboe Commissioner of Health of the State of New York and his associates [40] Here one can find detailed information concerning a cancer control program professional and lay education case finding records and reporting pro

vention and cancer services An extensive bibliography on cancer care services lists sixteen official agencies at Federal state, and local levels including the voluntary health organizations and professional societies Even if adequately endowed it is highly improbable that a cancer clinic can long survive on an autonomic basis Or assuming that fortuitous circumstances make for financial independence it is highly improbable that even that will make it possible for such a clinic best to serve the interests of any considerable number of cancer patients unless some well conceived and carefully executed plan is developed utilizing all available resources of the community

Through the expenditure of millions of dollars the public campaigns of the voluntary health agencies have stressed education service and research to the extent that the majority of the reading public is distinctly cancer conscious Important as lay education may be there is little use in arousing public interest in cancer if organized cancer facilities for diagnosis and treatment are not available and if the profession in general remains apathetic toward its responsibility and the opportunities thus offered

To accomplish these ends and to establish and maintain professional control and scientific direction of cancer programs within specifically defined geographic areas it might logically follow that in such zones the Cancer Committee of the State Medical Society or a State Cancer Co ordinating Committee or even a Regional Cancer Committee of the American College of Surgeons might assume the role of cancer co ordinator extraordinary for that State Under such a plan a central committee might be formed composed of representatives of the medical profession and various voluntary health organizations and the State Department of Health Such a committee might act as the legislative division of the state cancer control program while the executive functions would logically remain with the cancer clinics and other programs and agencies involved This composite, policy forming body could exert its influence on the proper organization and conduct of cancer facilities throughout the state As a quasi comptroller of funds to be expended for cancer control within the state it might serve as arbiter of expenditures for lay and professional education research and service thus saving many dollars and much duplication of effort It might lend its strength and experience to vitalizing lagging co ordination of cancer teaching at either undergraduate or postgraduate levels and as part of its educational responsibility should organize symposia ' cancer days refresher courses, and similar teaching exercises provide a speakers panel make available moving pictures and other audio-visual aids and assist in providing and maintaining libraries on cancer in the larger teaching hospitals Such a body could be of inestimable value to the voluntary agencies in providing material for and assisting with their public campaigns for funds Seldom can any other single agency develop state wide uniformity of records or as effectively insist on legislative action to make cancer a reportable disease

The fundamentals of this plan of complete co ordination of all cancer organizations and facilities are already operating effectively in many regions Their success presupposes an entente cordial the fullest confidence an objective viewpoint and a sincerely altruistic purpose—that of improving the diagnosis and treatment of cancer and alleviating the suffering of its victims With that in mind these suggestions will work in any state of the Union and in that day will accomplish for the field of cancer control what the antibiotics have in the area of infectious disease

CHAPTER 3

The Organization of Cancer Detection Facilities

Charles S Cameron

The high order of curability of the most common cancers under optimal conditions of early diagnosis and adequate treatment indicates that improved control of the disease lies to a substantial degree in earlier diagnosis

An endeavor to achieve early diagnosis has been undertaken in the United States since 1913 through a program of public education which with increasing vigor has sought to inform laymen generally of the early signs and symptoms of cancer and of the importance of prompt medical consultation An improved understanding of the natural history of cancer made it clear that early as measured by the onset of signs and symptoms was not necessarily early as measured biologically It then seemed expedient to attempt the detection of cancer in its subclinical or silent phase that is in presumably healthy persons From this concept the cancer detection center has emerged as a clinic where apparently well persons may be examined with special emphasis on the indentification of subclinical cancer and of precancerous states

The place the cancer detection program holds in the entire cancer control program may be conceptualized in Figure 3 1 In this chart the natural history of cancer is indicated along the horizontal axis as the chronological development of a cancer from a single cell through a noninvasive stage an invasive stage followed by local spread and eventually to regional lymph node involvement distant metastases and finally widespread metastases Although the biological time indicated in the chart is fairly regular this is an oversimplification as we know that the chronological time intervals between some of the adjacent stages is sometimes close to zero and sometimes several years depending on the growth characteristics of the individual tumor In fact we have only the most meager information about the average time interval between these successive stages The hope of cure in terms of percentage is plotted along the vertical axis and drops from a theoretical figure in the neighborhood of 100 per cent at the single cell stage to the neighborhood of 0 per cent with widespread metastases

Every aspect of the cancer control program has as one of its aims the detection of cancer farther and farther to the left that is earlier on the biologic time axis

HISTORIC BACKGROUND

In 1740 Vacher [4] reported the attempt of a prophetic French physician to promote a program for the detection of breast cancer stating

> Suddenly in 1734 the whole female population of Besançon was overcome by a fear that they were suffering from cancer of the breast or might be so affected in the future This followed a surgeon s suggestion to the women of that city that they examine their breasts for lumps The sequel to this announcement was that all women examined their breasts so often and so long and squeezed them so much that a certain number really developed lumps which were subsequently speedily removed with the greatest success by the surgeon

In 1922 a number of temporary clinics were set up in Pennsylvania during the week of the annual fund raising campaign of the American Cancer Society the purpose of which was to examine all comers specifically for cancer Reliable results were reported from seven of these clinics 856 persons were

examined 146 were considered to have pre cancerous conditions 40 had early cancer and 19 had late cancer no evidence of cancer or its precursors was found in the remaining 681 In the words of the anonymous editor of these data 'To have allayed the fears of these 681 men and women was in itself worth much effort The 146 with precancerous conditions or early cancer were given a prospect of cure which they would not have had otherwise This represents a finding of 66 6 cancers per 1000 persons examined—a rate much higher than that found in examining symptomless persons and about the same rate of finding of cancer among those with the common danger signals

In the same year 1922 the Liberty Mutual Insurance Company made arrangements to give its policyholders free physical examinations and diagnostic services for suspected cancer at the Collis P Huntington Memorial Hospital in Boston In 1931 another organized attempt to examine large numbers of persons for cancer was made in Germany with the opening of a special clinic for women

In 1937 Dr Elise L Esperance established the Kate Depew Strang Cancer Prevention Clinic in the Infirmary for Women and Children in New York City where only presumably well persons were examined,

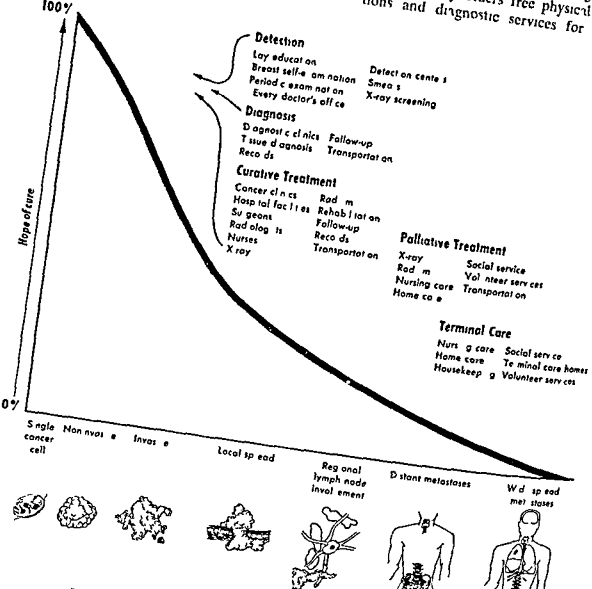


Fig 3 1 Service needs of cancer patients in various stages of the disease

primarily for cancer this marked the opening of the first cancer detection facility The following year Dr Catherine Macfarlane of the Women s Medical College and Hospital of Philadelphia undertook the periodic examination of 1000 apparently healthy women for the special purpose of uncovering unsuspected neoplasms of the pelvis and breast as the first step in a long range effort to detect the first evidences of cancer in these sites

By 1945 the number of cancer detection programs had grown to the point where it seemed advisable to formulate standards of operation and a system of approval similar to those provided to Cancer Clinics by the American College of Surgeons for the encouraging of high levels of professional performance In 1946 the American College of Surgeons agreed at the suggestion of the American Cancer Society to draw up such standards to undertake periodic inspection of the centers known to be in operation and to publish annually a list of centers approved *

Today there are some 250 cancer detection centers operating in the United States They examine several thousand persons each week They vary widely in methods of operation The oldest of the centers has passed its nineteenth anniversary most of them however have been operating for about 9 years

THE PURPOSES OF THE CANCER DETECTION CENTER

The primary purposes of the Cancer Detection Center were originally twofold

1 To find cancer earlier than it would otherwise be detected that is as a case finding technic This includes also the preventive aspects that is the detection of precancerous conditions (Figures 3 2 and 3 3)

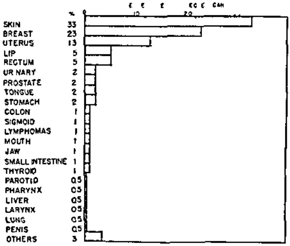


Fig 3 2 Cancers found in detection center examinations by s te (*From Detection Center Survey Report American Cancer Society 1949*)

2 As an educational device to teach people the value of periodic physical examinations The other benefits of the Cancer Detection Center include

3 The educational value to the medical profession in demonstrating the desirability of the periodic examination and the extent of examination offering maximum returns This applies both to the medical student and to the practicing physician

4 The research value of having a group of apparently well persons on whom to test various screening procedures and diagnostic

* The minimum standard for cancer detection centers [2] prepared by the College stated

1 *Organi ation* A specific plan for the organization and conduct of the center shall be approved by the County Medical Society before the project is made effective and the Society shall appoint a Medical Advisory Committee for guidance of the staff The detection center shall be conducted in a ho pital approved by the American College of Surgeon or in the outpatient department of an approved medical school or under conditions per mitting compliance with the other features of this tandard The medical staff shall adopt rules regulations and policies governing the profes ional work of the center and shall review and analyze their clinical experience at regular inter vals In addition to the medical staff which shall include representatives of the various branches of the medical profes ion a secretary nur e and medical social worker shall be avail able for the purposes of the center

Equipment The equipment shall be adequate for a complete physical examination

3 *Patients* All applicants within specified geographic limits shall be admitted except those who are already under treatment. Some detection centers may be restricted to males and others to females

4 *I ecords* There hall be maintained adequate complete records of examinees which shall include identification data occupation history physical examinations with indicated laboratory examina tions summary and disposition of such per ons

Disposition of Examinees Per ons who re quire furth r diagno tic procedures th n are fur ni h d by the center or for wh m tr atm nt is in licat d shall be referred b ck to th ir phy i cian If they have no physician they shall b given a li t of physi ians clinic or ho pital from which choice may be ma le and to whi h th find ings of the center shall b furn sl ed The l te ti n nt r shall se k from the phy i i n clinic or h pital a record of final diagn is tr atm nt and f llow up Examine s shall b r ari l t l ve peri lic phy ical examinati n a indi t l

f Fees A ntrit uti n of a specific l sum of m n y t v ry l xp n of the center shall be re quir l f ex m ine who are al le to pay

devices for the detection of cancer

5 The value accruing to the health of the *community through the discovery of many* conditions unrelated to cancer that can be treated with varying degrees of benefit

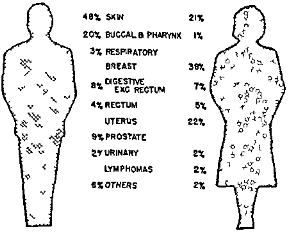


Fig 3 3 Cancers found in detection center examinations are shown by site and sex (From Cancer Detection Survey Report American Cancer Society 1949)

THE OPERATION OF CANCER DETECTION CENTERS

Selection of Examinees

By definition the Cancer Detection Center is intended for the examination of symptom free persons only Obviously the term symptom free is relative and has meaning only in terms of the degree to which the prospective examinee is interrogated prior to being accepted as a client In one study [1] in which prospective examinees were carefully questioned as to whether or not they manifested any of the danger signals of cancer and accepted only if they did not show these symptoms but referred to their physician or to a diagnostic clinic if they did an analysis was made of a follow up of both groups In the symptom free group the cancer rate was 3 5 per 1000 In the group with one or more danger signals the rate was 65 7 per 1000

Another problem stems from the fact that women outnumber men in the ratio of 3 to 1 among applicants for a cancer detection examination This is partly because most centers operate during the daytime when it is more convenient for women than for men In those places where the center operates during evening hours the discrepancy between the sexes is not as marked

From the point of view of case finding the older age groups are much more productive than the younger age groups Table 3 1 summarizes the experience in 125 different centers based on examination of over 50 000 persons [3] It may be seen that the positive findings rise from a low point of 1 2 cases of cancer per 1000 among those under thirty to a high of 29 3 per 1000 for those aged sixty and over It should be noted however that it is only with respect to cancer case finding that it is desirable to restrict examina*tions to those in the highest age groups* For educational purposes or for research purposes the younger age groups may be as important as or even more important than the older age groups

The Extent of the Examination

The physical examinations may be summarized in the three types listed with their component parts in Table 3 2 the complete examination the intermediate examination and the streamlined or limited examination In a consideration of the components of the examination to be performed in a cancer detection center no mention is made of other commonly employed features of a physical examination such as auscultation of chest and heart determination of blood pressure reflex testing serodiagnostic tests etc Obviously the extent of the examination depends on what the examiner is trying to find—or to eliminate If the purpose of the examiner is to find any and all departures from normal then considerations of time cost and availability of technical personnel limit its application to relatively few further *such additional* procedures have little or no bearing on cancer If the purpose of the examination is to indoctrinate the examinee as to what a thorough cancer detection survey should be as a first step in establishing the habit of periodic physical examinations then the complete examination is offered The same holds when the objective is to demonstrate the value of cancer case finding methods to medical students and practitioners

If the objective is to detect as much cancer as possible in a population then the extent of

TABLE 3 1 —SUMMARY OF PROVED CANCERS CLIENTS EXAMINED AND RATES PER 1000 BY AGE AND SEX FOR 125 CANCER DETECTION CENTERS

	Males		*Females*		*Total*	
Age	*Proved Ca / No Clients*	*Rate per 1000*	*Proved Ca / No Clients*	*Rate per 1000*	*Proved Ca / No Clients*	*Rate per 1000*
Under 30	2 / 1551	1 3	6 / 5339	1 1	8 / 6890	1 2
30-39	10 / 3763	2 7	27 / 12981	2 1	37 / 16744	2 2
40–49	10 / 3583	2 8	56 / 11402	4 9	66 / 14985	4 4
50–59	29 / 2101	13 8	75 / 6846	11 0	104 / 8947	11 6
60 & over	58 / 1245	46 6	64 / 2917	21 9	122 / 4162	29 3
All Ages	121* / 12243	9 9	245† / 39485	6 2	406‡ / 51728	7 8

* Includes 1[illegible] male cases with age not stated
† Includes 1[illegible] female cases with age not stated
‡ Includes the 12 male and 17 female cases with age not stated and 40 additional cases with sex not stated

TABLE 3 2 —RECOMMENDED EXTENT OF EXAMINATION TO BE EMPLOYED IN CANCER DETECTION CENTERS AT THREE DIFFERENT LEVELS OF COMPLETENESS

Complete	*Intermediate*	*Limited*
Skin	Skin	Skin
Lip	Lip	Lip
Intraoral	Intraoral	Intraoral
Nose throat (larynx)	Breast	Breast
Breast	Abdomen	Pelvis
Abdomen	Lymph node bearing regions	Rectum
Lymph node bearing regions	Pelvis	Chest film
Pelvis	Rectum	
Rectum Sigmoid	Urinalysis	
Chest film	Chest film	
Gastrointestinal x ray study		
Barium enema		
Urinalysis		
CBC		

the examination is determined by a consideration of (1) incidence in the various anatomic sites (2) time of professional and technical services necessary and (3) cost Under such circumstances attention is given to selected sites namely those that are frequent cancer loci examinable with ease and at low cost The limited examination presented in Table 3 2 appears to serve this objective

Other Operational Problems

THE MEDICAL HISTORY

In approximately half of the detection centers in operation the medical history is taken by the medical examiner in the remaining half it is taken by the nurse by a medical secretary and even in some instances by volunteers with special training If a complete examination is performed it is most desirable for the examiner to take the history In the briefer examinations a history taken by someone else and largely confined to the restricted anatomic sites being examined may be a great timesaver for the physician With some restricted types of examination a simple check list filled out by the patient with the assistance of the nurse or secretary if necessary has proved useful in pointing up the areas to be emphasized The forms to be used must be simple preferably of the check list type

THE BIOPSY

Whether or not it is proper for a biopsy to be taken at a detection center has been the subject of some controversy Many feel that the taking of a biopsy constitutes the definitive diagnostic procedure that belongs primarily in the hands of the physician who is to carry through and be responsible for the treatment of the patient Others feel that it is absurd for the detection center examination to identify suspicious areas to the point of recommending a biopsy and not have the authority to perform the biopsy and establish the diagnosis of a suspicious lesion As in so many other problems arising in the operation of a detection center the answer depends on the needs of the community in which the center is located and is best determined by the local medical society A compromise is to have the detection center take biopsies if failure to do so would be apt to result in undesirable delay

REFERRAL

Since the cancer detection center does not treat patients the problem arises as to the disposition of information about a patient collected by the center Normally a report is sent to the examinee s private physician including both the findings and the recommendations of the center Sometimes the examinee has no personal physician in which case a system of referral determined by the local medical society is employed for example naming one or more physicians from an approved rotating list In the case of indigent patients referral is directly to a clinic or to a governmental health and welfare agency responsible for treatment in such cases

REPEAT EXAMINATIONS

As an educational device the cancer detection center has the aim of developing in the public the habit of periodic physical examinations Since its capacity in terms of case load is limited it is difficult for the center to assume the responsibility for successive examinations of the same person If the initial examination has been successful from an educational point of view the examinee will return to his personal physician for subsequent examinations Even from a case finding point of view repeat examinations are less productive than initial examinations since the latter tend to uncover an accumulation of slowly growing and treatable cancers that have presumably been present for some time

For research purposes carrying on successive examinations has a great deal of merit It must be recognized however that such a procedure tends to increase geometrically to the point at which no new patients can be accepted and the center becomes a facility for the repeated examining of a fortunate and select few having no special claims to this good fortune except that they were early arrivals

WAITING LISTS

One of the unfortunate aspects of the cancer detection center is that immediately

upon its establishment usually following a certain amount of publicity, there is a great demand for its use and a long waiting list develops Occasionally some misguided individual with a serious symptom that has been hidden from the secretary making appointments will wait six months to a year for an appointment at a center when the condition warrants an immediate diagnosis For this reason it is best not to allow a waiting list to get too long At the same time it is imperative that the person handling requests for appointments be both tactful and persuasive about referring those with symptoms to more immediate sources of diagnosis

FEES

The actual cost of a single examination varies from about $5 for a limited examination to $75–$100 for reasonably complete examinations In many centers the examinee pays either all this cost or a large portion of it However it must be recognized that true cost figures for the operation of detection centers are very difficult to obtain since the reported figures reflect varying practices in accounting procedures more than they represent actual expenditures for the operation of the centers

Organization

RELATION OF THE CANCER DETECTION CENTER TO MEDICAL PRACTICE

The reasonable starting point in organizing a cancer detection center might be the Minimum Standard formerly proposed by the American College of Surgeons at the request of the American Cancer Society and reproduced on page 26 Although the program of standardization of the detection centers was discontinued by the College in 1953 its principles remain sound

PERSONNEL

Physicians nurses medical social workers technicians secretaries clerks telephone operators laboratory cleaners and janitors are required in numbers appropriate to the volume of examinations Personnel varies from that of the small community center with one physician assisted by one nurse who is responsible for records and follow up to that of the metropolitan center with as many as 30 full time and 50 part time physicians and corresponding numbers of nurses technicians secretaries etc

Medical personnel consists of a director of the center engaged full or part time in its administration and operation and its requisite number of examining physicians Qualifications of a director preferably include special interest and experience in clinical cancer The choice of his physician assistants will depend largely on the basic concept of the purpose of the center whether educational or case finding and contingent thereupon whether the examination is to be complete or limited Where reasonably thorough investigation of the patient site by site is the policy it is the practice of many centers to provide a staff of specialists each in charge of a cubicle or room through each of which every patient passes successively The variety of specialists to be represented will be determined often by their availability and also by the practical consideration of what each can hope to accomplish under the circumstances For example in view of the elaborate nature of a complete urologic survey the urologist s role would be limited to a simple examination of the external genitalia and the prostate functions that can be assumed adequately by the surgeon examiner who will be examining the rectum digitally anyhow Similarly the infrequency of neoplasms of the nervous system render the services of a neurologist impractical Where specialists are responsible for the examination of each patient those most frequently designated are internists surgeons gynecologists dermatologists and otorhinolaryngologists Where a less extensive examination is the policy a similar staff of specialists may be utilized although it is more common to rely on general practitioners qualified to execute the designated procedures In the latter case it is usual for the entire examination to be performed in one room or cubicle by a single examining doctor who may call for consultation with an attending specialist when abnormal findings are encountered When the center is housed in or near a medical school it may be effectively used for teaching physical diagnosis In re

turn the medical students after being prop erly trained can assist in the routine of examination under close supervision

Nurses in suitable number are recruited from the outpatient clinic of the hospital in cally to refuse patients with symptoms and to refer them to the proper source of medical service Clinic aides to perform such duties as routing patients instructing them as to disrobing changing linen and writing charge and

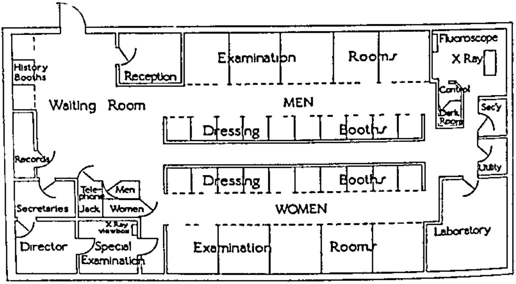


Fig 3 4 Floor plan for cancer detection center (*Adapted from* Strong Cancer Prevention Clinic Memorial Center for Cancer and Allied Diseases)

which the center operates and when size and work load suggest it a nursing supervisor should be designated For interchangeability according to changes in work load each nurse should be trained to competence in all posi tions in the center When centers are set up in facilities other than hospitals as in health centers or mobile units public health nurses may be engaged A nurse should be assigned responsibility for the collection of all labora tory specimens and for their delivery to the proper laboratory section

Follow up of patients with positive or suspi cious findings is clearly of importance and since such patients are without complaints and symptoms such follow up often calls for tact persuasiveness and persistence if it is to be effective Medical social workers and public health nurses are the logical choices for this assignment although the initial (mail) efforts may be the responsibility of the center s secretary

Receptionists and telephone interviewers must be courteous and resourceful have a thorough understanding of the policies and functions of the center and be able diplomati appointment slips are sometimes provided by local units of the American Cancer Society as part of their volunteer services Cured cancer patients often make enthusiastic volun teers or employees

While nurses social service workers labora tory technicians secretaries and housekeep ing employees are paid for their services at prevailing salary rates and on an hourly or weekly basis there is not uniform opinion as to whether the staff doctors should be paid In some centers the physician s services are held to be the equivalent of his services in the familiar outpatient department for which he receives no compensation other than ex perience and distinction Others recognizing that the doctor s service to the detection center is in addition to his traditional role of caring for the sick and that many examinees choosing the center s services can well afford to pay for them reimburse physicians for their time at an hourly rate or as is commoner on the basis of a fixed fee per session

Rooms for reception of examinees history taking physical examination x ray records etc should be laid out so as to minimize con

fusion from backtracking the flow of examinees The accompanying floor plan Figure 3-4 adapted from the Strang Cancer Prevention Clinic New York City is adequate for over one hundred examinations a day Several state organizations have mobile units for use in rural communities

of physiologic measurements for comparison with cancer patients They are closer to the age group of cancer patients than are most control groups and at the same time are not suffering from the severe illnesses encountered when a control group is selected from hospital patients

TABLE 3 3 —SUGGESTED EQUIPMENT FOR DETECTION CENTERS ACCORDING TO EXTENT OF THE EXAMINATION

Complete	*Intermediate*	*Limited*
Magnifying glass	Magnifying glass	Magnifying glass
Centimeter rule	Centimeter rule	Centimeter rule
Fenestrated tongue retractor	Fenestrated tongue retractor	Head mirror or lamp
Laryngeal mirrors	Head mirror or lamp	Vaginal specula
Nasal specula	Vaginal specula	Bulb suction pipette
Head mirror or lamp	Bulb suction pipette	Sigmoidoscope
Transilluminating light	Sigmoidoscope	Dressing forceps
Vaginal specula	Dressing forceps	
Bulb suction pipette		
Sigmoidoscope		
Dressing forceps		

Equipment includes the usual furniture for examining rooms and offices including typewriters files stationery and record forms The suggested lists of portable equipment items (Table 3 3) are considered minimal for the three types of examination—complete intermediate and limited—and include only items actually employed by the examining physician and the nurse omitting those required in laboratory and x ray phases of the examination

Records should be as simple as is consistent with obtaining all desirable data Record blanks should be so devised that statistically valuable data may be derived and classified readily

RESEARCH POTENTIALITIES OF THE DETECTION CENTER

The persons who come to a cancer detection center provide an excellent group on the basis of which norms may be obtained on a variety

Screening Tests

A screening test for cancer may be defined as *any simple inexpensive procedure that may* be used to rule out the possibility of cancer in a large portion of the cancer free population without at the same time ruling it out in very many persons who do have cancer Whether such a test that would be sensitive to most forms of cancer is theoretically possible is open to question A number of blood tests have been proposed but thus far none has been proved to meet the necessary requirements for practical usefulness

A more promising approach appears to be the use of a variety of screening procedures that are site specific Most prominent among these is the examination of various body exudates and secretions by cytologic methods In addition testing for occult blood in the stool or urine gastric analysis for achlorhydria and the less expensive forms of x ray

examination such as chest microfilms and gastric photo fluoroscopy are valuable in indicating when more thorough examination may be profitable

The Study of the Aging Process

Since 1900 the proportion of the population over the age of forty for example has increased by 50 per cent Certainly the study of the changes that take place both in health and in disease in a group of cancer detection examinees should add much to our knowledge of geriatrics

CHAPTER 4

Organization of a Program for Home Care of the Cancer Patient

Martin Cherkasky
and
Abraham Oppenheim

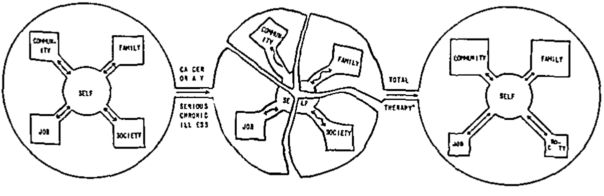
The steady increase in the life span and aging of the population has been paralleled by an increase in the incidence of chronic diseases including cancer This has made crucial today the problem of maintaining community resources adequate to meet the growing demands and requirements of the chronically ill

The problem is too vast to be solved by steadily increasing the number of hospital beds

On the basis of such considerations Montefiore Hospital New York City in 1947 began a home care program for patients with long term illness of whom a significant number have been cancer patients

The planning and developing of the Montefiore program was based on the concept of total therapy of which medical therapy forms but a part

In a program for the total care of the cancer patient we must (1) bring to the patient the best available scientific medical treatment that the illness demands (2) take into account that the patient is a social being whose relationships to his family and society may be severely disrupted by this illness (3) meet these multiple needs of the patient by providing several health workers functioning as a team This is necessary whether the program of medical care is provided on an in patient outpatient or in the home basis (see Figure 4 1)



A. FORCES CONTRIBUTING TO MAINTENANCE OF INDIVIDUAL.

B. DISRUPTION DUE TO SERIOUS ILLNESS WITH SELF DISTORTION

C. RECONSTITUTION OF THE INDIVIDUAL BY GREATER FAMILY AND COMMUNITY SUPPORT ETC. THOUGH JOB AND SOCIETY CONTRIBUTE LESS.

Fig 4 1 The effect of total therapy on the cancer patient

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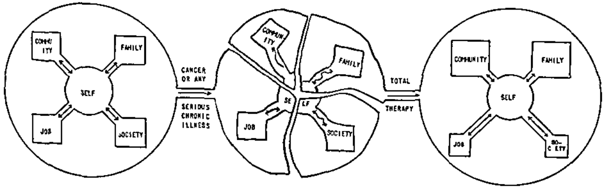

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Fig 4 1 The effect of total therapy on the cancer patient

SELECTION OF PATIENTS

Before a hospitalized patient was accepted for home care both a medical and a social evaluation were made The former consisted of a thorough study of the patient and his record while in the hospital to determine whether his medical needs could be adequately met within the framework of the home Except for patients who required major operations extensive radiotherapy major diagnostic work up and extensive nursing care there were very few patients who medically could not adequately be cared for in the home after they had received their definitive therapy in the hospital

After medical acceptance the social worker evaluates the patient An understanding of all factors may indicate that the patient will need considerable help if he is to be able to adjust to and be cared for at home For example The hospital is for the patient a relatively protected environment For the patient who has been hospitalized for a long time the thought of going home of leaving a situation in which he has gradually had to learn a totally new set of adjustments may be greeted with hesitance or reservation even if he wants to leave the hospital

The social worker speaks with members of the family to determine primarily whether a family wants the patient at home The natural love of one member of the family for another cannot be assumed since in many cases it unfortunately may be lacking A differentiation must be made between a family that does not want the patient and prefers him out of the way and in an institution and the family that hesitates to take the patient home because they think that some other place would be better for him and could care for him more adequately This latter family with guidance and understanding and with support and direction frequently turns out to be an excellent family unit and one in which home care can function most successfully

Experience has taught that where the patient is medically quite suitable for home care but where the social situation is unfavorable the patient cannot be adequately cared for in the home Also included in the social evaluation is a survey of the physical facilities in the home This is not important except when the physical setup is actually inimical to the health and welfare of the patient

ADMINISTRATIVE STRUCTURE OF THE HOME CARE

The Home Care Department is part of the Division of Social Medicine It is administered by a salaried physician who devotes his full time to the program Half of this physician's time is devoted to administrative problems and half to patient care There are three other internists each of whom devotes 15 hours a week to patient care This staff of four physicians is sufficient to meet the needs of approximately 85 patients in the home

Consultations are provided on a fee for service basis with the senior attending staff of the hospital rendering these services The most frequent specialties used are dentistry pathology radiology orthopedics and neurology The cancer patient is seen in the home by a physician on an average of once every five days To meet the needs of an average census of 85 patients requires in addition to the physicians noted above three full time social workers one and a half occupational therapists one physiotherapist and two and a half secretaries Housekeeping help is obtained from various sources and is used on the average of between five and ten hours per week Nursing care is provided through the Visiting Nurse Service of New York where the regular per visit fee is paid On the average cancer patients have been seen about once a week by the nurse but in some instances a nursing visit a day has been required

The total annual budget is about $90 000 and the main areas in which this money is expended are as follows

	Per Cent
Physician services	33
Social workers occupational therapists physiotherapists secretarial help housekeeping services	35
Patient and employee transportation drugs laboratory tests	12

Medical equipment and ambulance service	6
Visiting Nurse Service	10
Miscellaneous expenses and supplies	4
	100

FUNCTIONING OF THE PROGRAM

Within 24 hours after return to the home the patient is seen by a physician who carefully re evaluates him medically to determine how often he needs to be visited on a regularly scheduled basis

The following services are available to the patient in his home

1 *Medical Service* This is available around the clock seven days a week Specialists such as orthopedists ophthalmologists and surgeons are available for the patient in his home Many medical procedures such as paracentesis and blood transfusions can readily be done in the home

2 *Nursing Service* The public health nurse is an integral member of the team The Montefiore Hospital Home Care Program has a contract with the Visiting Nurse Service of New York whereby they provide most of the nursing care in the home for patients in the program An increasingly substantial part of the nursing care is being provided by students from the Montefiore School of Practical Nursing for whom this field work has become an integral part of the teaching curriculum In addition every patient whether he requires nursing or not is seen at least once by a member of the visiting nurse staff This is in the nature of a nursing consultation The nurse offers primarily two types of service (*a*) direct bedside nursing (*b*) what is probably much more important instruction of members of the family in the simple nursing technics that the average individual can master and that are of inestimable benefit to the patient Members of the family are taught how to give baths how to give hypodermics how to test urine and other similar procedures To facilitate and maintain a close working relationship a part time nurse coordinator is part of the team Conferences and discussions about the patient take place weekly or more often and the doctor nurse and the social worker discuss the problems that face the patient

3 *Social Service* The social worker who made the evaluation of the patient in the hospital continues to provide care for the patient in the home She continues to help both the patient and his family with the social and emotional problems arising out of the illness she assumes responsibility for referring the family when needed to a community agency and is generally concerned with any social problems that have an impact on the patient s welfare The social worker with her training and understanding is able to guide the family through its initial difficult period to interpret to the family what the illness means in terms that they can understand to help with problems such as arranging for the wife to be able to go out and work or any other problems that have to be met to provide a better family a better home life and a more suitable atmosphere for the care of the patient

To meet all the needs of the patient other services are provided in addition to those of the doctor nurse and social worker who form the primary team

4 *Housekeeping Service* Housekeeping service is provided 5 to 10 hours a week This is often very helpful since many of the patients who would otherwise have to remain in the hospital can well be taken care of at home if there is some one to help with the heavy housework

5 *Occupational Therapy* This is provided by trained therapists working in conjunction with the doctors and others so that the activities are designed not only for recreational but for therapeutic value as well Recreational pursuits are an essential and integral part of any program dealing with the long term sick

6 *Physical Therapy* Working under the direction of physicians especially trained in physical medicine the therapist carries out many procedures in the home such as massage baking muscle re-education and walking exercises The process of rehabilitation is a continuous one and is directed toward enabling the patient to make the best use of those facilities still remaining to him There are some who feel that to attempt to rehabilitate a patient who is going to die from cancer is

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a waste of money and effort This attitude of course is completely unacceptable to those who have devoted their lives to the care of people whether the prognosis is good or bad

7 *Medication and Equipment* All drugs and equipment are provided for the patient including needles syringes bedpans wheel chairs braces artificial limbs etc Of great help in maintaining a patient in the home is the availability of a hospital type of bed

8 *Laboratory Services* These are provided either by bringing specimens such as blood or urine to the hospital for analysis or by bringing the patient to the hospital if necessary In the event that a patient at home requires a procedure such as extensive x ray series that can only be carried out in the hospital then the patient is brought to the hospital for such a procedure The appointment is made in advance and if the patient is ambulatory or semiambulatory he may be brought by taxicab if bedridden he is brought by means of an ambulance The separation of the patient from the hospital is never allowed to deprive the patient of any service that the hospital can give If the service cannot be brought to the patient the patient is brought to the service

9 *Transportation* Transportation to and from the hospital for both patient and personnel is provided

To illustrate the selection of a home care patient and the definitive care, it might be well to have you follow a typical case

The patient a fifty eight year old white female had had a left radical mastectomy plus postoperative irradiation three years prior to her admission to Montefiore Hospital She remained well for one year then she began suffering pain in her left arm owing to metastases to the left humerus and both tibiae She was given the usual course of testosterone therapy with marked relief of pain and with healing in the metastatic sites She then sustained a pathologic fracture of the right femur was confined to bed and admitted to the hospital where she received hormonal therapy Physical examination at the time of discharge to Home Care revealed a well healed left supraclavicular fossa The left arm showed swelling with deformity and limitation of motion The right hip was swollen deformed and tender The limb was inverted and fore shortened The right lower limb showed deformity and swelling above the right knee Radiation therapy was not considered feasible for this patient The orthopedists did not feel it wise to immobilize her with casts She was bedridden and unable to be moved without undue pain Although her medical condition made the possibility of home maintenance seem questionable the patient was accepted for home care in view of her urgent request to be home and her increasing depression on remaining in the hospital

The social evaluation for home care revealed that the patient lived in a one story cottage with her son and husband both of whom were employed She had always been an energetic, vigorous person whose activities extended beyond the management of her home and raising of three children into multiple community affairs She had worked and maintained her personal independence so that coming into the hospital and being bedridden and helpless were very difficult for her to face and accept Beyond this she had to endure great and almost constant physical pain and despite her courageous efforts to keep cheerful and optimistic she became increasingly depressed and wondered if she would ever be able to do anything for herself again An underlying feeling that she was hopeless was for this patient only accentuated by the depressing atmosphere of the ward She became increasingly restless and discouraged and pressed for discharge Plans were made so that the patient would have some housekeeping help and it was arranged that her meals would be left on a table at her bedside so that she could manage until her family came home in the evening Several friends also agreed to drop in periodically during the day to help her if needed

In the first few weeks of home care the social worker visited regularly three times a week and in this period the patient was finally able to release much of her deep tension She needed and was given a sense of sharing in the medical plans treatment was explained her questions were answered and a great deal of reassurance and support were given by the total program After about a month at home her mental outlook became better and she improved physically She requested that the

doctor consider trying to put her in a wheel chair

The patient was seen on a consultation basis by the Neoplastic Orthopedic and Radiation Therapy services It was agreed to supply her with a wheel chair She was continued on hormonal therapy and despite the severe limitation of movement in the various ex tremities resulting from metastases she man aged to create a close to normal existence in her wheel chair

Some healing of the pathologic fractures occurred she was able to move both lower extremities and she began to assume many responsibilities She was not satisfied to de pend upon others to assist her into the chair and devised a system whereby despite her paraplegia she could do it alone She lowered the back of the chair onto the bed so that it formed a bridge from the bed to the seat and from her sitting position maneuvered herself gradually into the chair This was the first step toward achieving her independence Now that she could get around in a wheel chair she was determined to take over her house hold again And she did She wheeled into the kitchen and from the chair prepared all the meals for the family from her chair she baked washed clothes ironed washed her floor swept made the beds straightened the house Her family bought her long wooden scissors like tongs with rubber ends with which she picked up things from the floor or from high places When she was through with the house work she wheeled into the garden and hung up the family wash that she had done She weeded the garden and planted flowers with her scissors Mrs P even complained to the worker and doctors that the day was not long enough

The patient eventually became progressively worse and about one month prior to her death was completely bedridden Even at this time she wanted to be at home and resisted return to the hospital until it was absolutely neces sary

What are the results of our program? It has been gratifying that this program has met by the team approach the multiple needs of the patient Of considerable importance to the community has been the fact that the Home Care Program not only meets the needs of the patient but costs much less than institutional care The cost per patient day was about \$3 50 as compared to a patient day cost at Montefiore Hospital of more than \$23 00 The Home Care cost includes all salaries and services such as fees for the doctors services housekeeping services occupational therapy physical therapy as well as all materials and supplies

Of considerably greater importance how ever is the value of this program to the patient his family and the community The hospital of necessity has a discipline that is essential for efficient function but this dis cipline is not always in accord with the wishes needs or desires of any one individual patient After the hospital has given the maximum to the patient the loss of the little conveniences to the patient becomes more and more impor tant With even the barest physical facilities a good home is in many instances far superior for the care of the patient to the best appointed hospital

Diagnosis and Pathology

Diagnosis and Pathology

CHAPTER 5

The Microscopic Grading of Cancer

Albert C Broders

The variability in the malignancy of different kinds of cancer and of the same kind in different situations has long been known Thus squamous cell cancer was known to be more malignant than basal cell cancer melanotic cancer was known to be more malignant than the other two types squamous cell cancers of the uterine cervix were known to be of higher average malignancy than squamous cell cancers of the lip and adenocarcinomas of the stomach were known to be of higher average malignancy than adenocarcinomas of the body of the uterus However when it came to carcinomas of the same type at the same site general appreciation of the variation of malignancy was until recently possessed by but few observers A carcinoma of the lip was considered a carcinoma of the lip a carcinoma of the stomach a carcinoma of the stomach and a carcinoma of the breast a carcinoma of the breast and usually nothing more Experienced and discerning physicians however had observed that papillary polypoid or elevated carcinomas were less malignant than those that were flat or infiltrating This observation was fully appreciated by the late W W Mayo when he postulated A cancer that comes to you is less malignant than one that goes away from you

EARLY CONCEPTS CONCERNING VARIATIONS IN THE MALIGNANCY OF TUMORS

The possibility of detecting the varying malignancy of carcinoma by microscopic examination was foreshadowed by Virchow [14] in 1858 who said Cancer is not malignant because it contains heterologous cells nor cancroid benignant because its cells are homologous—they are both malignant and their malignity only differs in degree"

Beginning in 1890 Hansemann (1890 1902) postulated that noncancerous epithelial cells change into cancer cells by a process called anaplasia (backward to form) a term that Hansemann himself suggested To him anaplasia not only represented the process by which the noncancer cells are transformed into cancer cells but the process by which the mature unfertilized ovum is developed from a somatic cell

In the course of his studies Hansemann raised the question as to whether the degree of malignancy of a cancer could be determined from the histologic structure and thought that the answer to this question probably could be found in a study of the anaplasia as he had observed that cancers with the most marked anaplasia also showed the greatest tendency to metastasize His studies revealed that one almost never failed to find recurrence or metastasis in cases in which the neoplasms were markedly anaplastic on the other hand if the neoplasms showed only a mild degree of anaplasia there were found either no recurrences and metastases or recurrences and metastases with stronger or more marked anaplasia than found in the original tumor In view of Hansemann s observation that a tumor can change from a lower to a higher grade of anaplasia he was of the opinion that one could tell more about the prognosis in cases of neoplasm with marked anaplasia than one could tell in cases of neoplasm in which there is little or no anaplasia

AUTHOR S METHOD OF MICROSCOPIC GRADING

The system of grading cancer is as follows Grade 1 epithelioma is one in which differentiation ranges from almost 100 per cent

Fig 51 Adenocarcinoma Grade I of rectum

Fig 52 Adenocarcinoma Grade I of breast

Fg 53 Adenocarcinoma Grade I of stomach

Fig 5-4 Adenocarcinoma Grade I of endometrium

Fg 5-5 Squamous-cell epitheli oma Grade I of l p

Fig 5-6 Squamous-cell ep thel oma G ade I of sk n

Fig 57 Squamous-cell ep thel oma Grade I of pen s

Fig 58 Squamous-cell ep theli oma Grade I of ur nary bladder

Fig 5-9 Adenocarcinoma Grade II of breast

Fig 5-10 Adenocarcinoma Grade II of rectum

Fig 5-11 Adenocarcinoma Grade II of stomach

Fig 5-12 Adenocarcinoma Grade II of thyroid

Fig 5-13 Squamous-cell epithelioma Grade II of ear

Fig 5-14 Squamous-cell epithelioma Grade II of larynx

Fig 5-15 Squamous-cell epithelioma Grade II of gallbladder

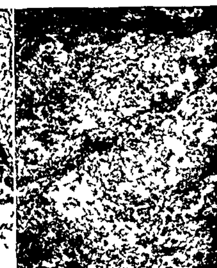


Fig 5-16 Squamous-cell epithelioma Grade II of cervix uteri

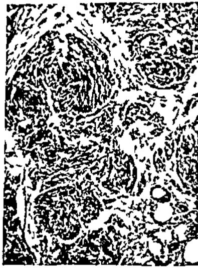


Fig 5 17 Adenocarc noma Grade III of thyroid gland

Fig 5 18 Adenocarcinoma Grade III of breast

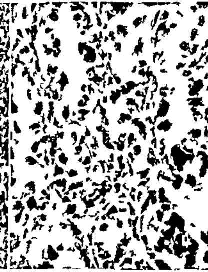


Fig 5 19 Adenocarcinoma Grade III of bronchus

Fig 5 20 Adenocarcinoma Grade III of stomach

F g 5 21 Squamous-cell ep theli oma Grade III of skin

Fig 5-22 Squamous-cell ep theli oma G ad III of ur nary bladder

Fig 5 23 Squamous-cell ep theli oma Grade III of female urethra

Fig 5 24 Squamous-cell epitheli oma Grade III of cervix ut ri

Fig 5 25 Adenocarcinoma Grade IV of thyroid gland

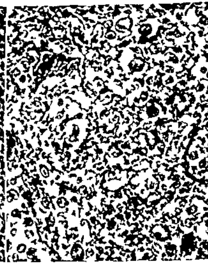


Fig 5 26 Adenocarcinoma Grade IV of breast

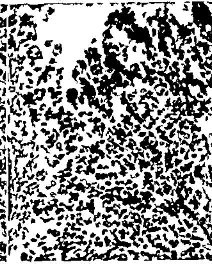


Fig 5 27 Adenocarcinoma Grade IV of stomach

Fig 5 28 Adenocarcinoma Grade IV of rectum

Fig 5-29 Squamous cell epithelioma Grade IV of skin

Fig 5 30 Squamous cell epithelioma Grade IV of tonsil

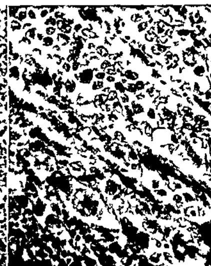


Fig 5 31 Squamous cell epithelioma Grade IV of urinary bladder

Fig 5 32 Squamous cell epithelioma Grade IV of cervix uteri

to 75 per cent, and undifferentiation from almost nothing to 25 per cent A Grade II epithelioma is one in which differentiation ranges from 75 per cent to 50 per cent and undifferentiation from 25 per cent to 50 per cent A Grade III epithelioma is one in which differentiation or self control ranges from 50 per cent to 25 per cent and undifferentiation from 50 per cent to 75 per cent A Grade IV epithelioma is one in which differentiation or self control ranges from 25 per cent to practically nothing and undifferentiation from 75 per cent to practically 100 per cent

A completely differentiated cell of an epidermoid carcinoma is one in which the entire cytoplasm is keratino hyalinized or keratinized and the nucleoplasm has become eccentric and degenerated Such cells may be arranged in a discrete manner but are usually conglomerated in the form of pearly bodies I believe one can say that they have reached a state of absolute differentiation in other words they have arrived at a point where they can neither dedifferentiate nor reproduce

In a partially differentiated cell of a squamous cell carcinoma the cytoplasm is not completely keratino hyalinized or keratinized The cytoplasm is usually disproportionately large in volume in comparison with the nucleoplasm which often appears actually to have decreased so that it is not more voluminous than the nucleolus observed in some cells of the same type of carcinoma In this cell the nucleoplasm usually appears as a small spheroidal or oval mass situated about the center of the cytoplasm and it does not show evidence of encroachment and degeneration Such a cell has differentiated to the point that its reproductive capacity is reduced to the minimum The production of melanin in melanocarcinoma is evidence of differentiation just as is the production of keratin in squamous cell carcinoma

The range of dedifferentiation and differentiation in basal cell carcinoma is usually slight. The cells of a basal cell carcinoma not infrequently partially or completely differentiate toward the squamous-cell type as manifested by keratinization and formation of pearly bodies Conversely they may partially differentiate in a glandular direction however for the most part they retain the characteristics of basal cells

The partially differentiated cell of an adenocarcinoma has a spheroidal oval or spindle shaped nucleus usually situated at the base of a columnar or cuboidal cell and as in the squamous cell carcinoma it is relatively small in comparison to the cytoplasm The cytoplasm of such a cell may or may not contain a secretory product If the cell has reached a state of complete differentiation the nucleoplasm not infrequently will have disappeared as is seen in mucoid adenocarcinoma

In contrast to partially and completely differentiated cells it is also necessary for the accurate grading of carcinoma and other malignant neoplasms that the microscopist be familiar with cells that are in a partially or completely undifferentiated state These cells vary in their degree of undifferentiation depending on the extent of dedifferention Cells in a state of mitosis or amitosis may be said to be in a state of partial or complete undifferentiation Since irregular or atypical mitosis of Hansemann in which the chromatin is arranged in a multipolar manner that is in Y star cross and similar formations is usually associated with carcinomas and other neoplasms of a high degree of malignancy it is safe to infer that these forms represent a state of extreme undifferentiation *Cells with* large spheroidal or irregular nuclei with or without prominent nucleoli in which the cytoplasm is decreased and the nucleoplasm increased in volume are familiar examples of undifferentiated forms The nuclei of undifferentiated cells frequently have marked avidity for the basic dyes

It is the aim of the microscopist in the grading of cancer and of other malignant neoplasms to estimate the proportion of cells that are partially or completely differentiated on the one hand and those that are more or less undifferentiated on the other

In prognosis of malignant tumors in general it goes without saying that well informed physicians take into consideration a number of factors however I do not hesitate to state that the grade of malignancy is by far the most important one As a rule the grades of

malignancy of carcinomatous neoplasms are in direct proportion to their proliferative infiltrative metastasizing and death dealing capacities The chief difference in the malignancy of different tumors or tumors of the same type depends on their cellular activity

Although the grading of cancer has its greatest value in prognosis it also is not infrequently of material assistance in determining the most effective therapeutic procedure in a given case For example Since Grade I cancer of the lip almost never metastasizes removal of the regional lymph nodes is not indicated

The following statistics (Tables 5 1 to 5 12) were compiled from the available information on 537 cancers of the lip 256 of the skin 473 of the genitourinary organs 362 of the cavities and internal organs of the head and neck 598 of the rectum and 3368 of the breast making a grand total of 5594 graded cancers

TABLE 5 1 —SQUAMOUS CELL EPITHELIOMA OF THE LIP

Postoperative Results According to Grade

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*All Grades*
Information					457 (88 56% of 516)
Living	50 (72 44% of 69)	159 (54 63% of 291)	26 (27 95% of 93)		235 (51 42% of 457)
Good result	50 (100% of 50)	157 (98 74% of 159)	24 (92 30% of 26)		231 (98 29% of 235)
Fair result		2 (1 25% of 159)	1 (3 84% of 26)		3 (1 27% of 235)
Poor result			1 (3 84% of 26)		1 (42% of 235)
Dead	19 (27 53% of 69)	132 (45 36% of 291)	67 (72 04% of 93)	4 (100% of 4)	222 (48 57% of 457)
Good result	17 (89 47% of 19)	72 (56 25% of 128)	11 (17 74% of 62)	1 (25% of 4)	101 (47 88% of 213)
Fair result	2 (10 52% of 19)	1 (78% of 128)			3 (1 40% of 213)
Poor result		55 (42 96% of 128)	51 (82 25% of 62)	3 (75% of 4)	109 (51 17% of 213)
Total results (dead)					213
Postoperative deaths		2	2		
Cause unknown		2	1		
Cause known but death took place too early to consider			2		
Total good result	67 (97 10% of 69)	229 (79 79% of 287)	35 (39 77% of 88)	1 (25% of 4)	332 (74 10% of 448)
Total fair result	2 (2 89% of 69)	3 (1 04% of 287)	1 (1 13% of 88)		6 (1 33% of 448)
Total poor result		55 (19 16% of 287)	52 (59 09% of 88)	3 (75% of 4)	110 (24 55% of 448)

Duration of Postoperative Life According to Grade

Information					448 cases
Living					235 cases

	Yrs	Yrs	Yrs	Yrs	Yrs
Good result					
Longest	20 00	21 10	17 62		21 10
Shortest	6 79	6 96	8 51		6 79
Average	13 60	13 04	12 0		13 10
Fair result					
Longest		18 98	13 61		18 98
Shortest		10 95			10 95
Average		14 97			14 51
Poor result					
Longest			10 52		10 52
Dead					213 cases

TABLE 5 1 *(Continued)*

Duration of Postoperative Life According to Grade

	Yrs	*Yrs*	*Yrs*	*Yrs*	*Yrs*
Good result					
Longest	18 40	18 38	11 30	3 73	18 40
Shortest	2 00	36	2 02		36
Average	9 00	7 32	7 10		7 55
Date of death not obtained		1			
Fair result					
Longest	9 98				9 98
Shortest	6 93				3 96
Average	8 45	3 96			6 96
P or result					
Longest		11 16	11 87	1 00	11 87
Shortest		06	03	37	03
Average		1 88	1 37	58	1 61
Date of death not obtained		1			

TABLE 5 2 —SQUAMOUS CELL EPITHELIOMA OF THE SKIN

Postoperative Results According to Grade

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*All Grades*
Information					215 (91 10% of 236)
Living	10 (50% of 20)	52 (35 61% of 146)	10 (26 31% of 38)	2 (18 18% of 11)	74 (34 41% of 215)
Good result	10 (100% of 10)	45 (86 53% of 52)	9 (90% of 10)	2 (100% of 2)	66 (89 18% of 74)
Fair result		7 (13 46% of 52)	1 (10% of 10)		8 (10 81% of 74)
Dead	10 (50% of 20)	94 (64 38% of 146)	28 (73 68% of 38)	9 (81 81% of 11)	141 (65 58% of 215)
Good result	10 (100% of 10)	37 (41 11% of 90)	7 (25% of 28)		54 (39 70% of 136)
Fair result		5 (5 55% of 90)			5 (3 67% of 136)
Poor result		48 (53 33% of 20)	21 (75% of 28)	8 (100% of 8)	77 (56 61% of 136)
Total results (dead)					136
Postoperative deaths				1	
Cause unknown		2			
Cause known but took place too early to consider		2			
Total good results	20 (100% of 20)	82 (57 74% of 142)	16 (42 10% of 38)	2 (20% of 10)	120 (57 14% of 210)
Total fair results		12 (8 45% of 142)	1 (2 63% of 38)		13 (6 19% of 210)
Total poor results		48 (33 80% of 142)	21 (55 26% of 38)	8 (80% of 10)	77 (36 66% of 210)

TABLE 5 2 *(Continued)*

Duration of Postoperative Life According to Grade

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*All Grades*
Information					215 cases
Living					74 cases
	Yrs	*Yrs*	*Yrs*	*Yrs*	*Yrs*
Good result					
Longest	13 15	20 52	16 38	13 35	20 52
Shortest	9 50	8 90	10 60	10 15	8 90
Average	11 38	12 71	13 22	11 75	12 54
Fair result					
Longest		16 20	15 70		16 20
Shortest		3 99			3 99
Average		10 79			11 41
Dead					141 cases
Good result					
Longest	13 00	15 00	12 10		15 00
Shortest	43	26	82		26
Average	5 69	5 92	7 06		6 03
Fair result					
Longest		10 85			10 85
Shortest		2 78			2 78
Average		6 97			6 97
Poor result					
Longest		11 19	4 16	2 96	11 19
Shortest		15	25	05	05
Average		2 04	1 16	1 23	1 71

TABLE 5 3 —SQUAMOUS CELL EPITHELIOMA OF THE GENITOURINARY ORGANS
Postoperative Results According to Grade

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*All Grades*
n					408 (92 72% of 440)
ing	11 (55 55% of 20)	26 (26% of 100)	32 (17 77% of 180)	7 (6 48% of 108)	76 (18 62% of 408)
Good result	11 (100% of 11)	25 (96 15% of 26)	32 (100% of 32)	7 (100% of 7)	75 (20% of 375)
Fair result		1 (3 84% of 26)			
Dead	9 (45% of 20)	74 (74% of 100)	148 (82 22% of 180)	101 (93 51% of 108)	332 (81 37% of 408)
Good result	3 (42 85% of 7)	14 (23 72% of 59)	9 (6 38% of 141)	3 (3 26% of 92)	29 (7 73% of 375)
Fair result	1 (14 28% of 7)				
Poor result	3 (42 85% of 7)	45 (76 27% of 59)	132 (93 61% of 141)	89 (96 73% of 92)	269 (71 73% of 375)
Postoperative deaths	1	11	6	5	
Cause unknown	1	2	1		
Cause known but took place too early to consider		2		4	
Total good results	14 (77 77% of 18)	39 (45 88% of 85)	41 (23 69% of 173)	10 (10 10% of 99)	104 (27 73% of 375)
Total fair results	1 (5 55% of 18)	1 (1 17% of 85)			2 (53% of 375)
Total poor results	3 (16 66% of 18)	45 (52 94% of 85)	132 (76 30% of 173)	89 (89 89% of 99)	269 (71 73% of 375)

Duration of Postoperative Life According to Grade

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*All Grades*
Information					408 cases
Living					76 cases
	Yrs	*Yrs*	*Yrs*	*Yrs*	*Yrs*
Good result					
Longest	18 47	19 06	21 06	13 82	21 06
Shortest	7 05	6 43	8 93	9 44	6 43
Average	12 21	12 69	13 13	10 48	12 63
Fair result					
Longest		12 48			
Dead					332 cases
Good result					
Longest	6 62	11 76	16 58	17 03	17 03
Shortest	4 86	1 16	1 93	4 93	1 16
Average	5 86	6 01	8 02	9 55	7 34
Fair result					
Longest	9 21				
Poor result					
Longest	2 87	12 22	10 68	4 80	12 22
Shortest	15	08	08	16	08
Average	1 86	2 23	1 56	1 20	1 55

TABLE 5 2 *(Continued)*

Duration of Postoperative Life According to Grade

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*All Grades*
Information					215 cases
Living					74 cases
	Yrs	*Yrs*	*Yrs*	*Yrs*	*Yrs*
Good result					
Longest	13 15	20 52	16 38	13 35	20 52
Shortest	9 50	8 90	10 60	10 15	8 90
Average	11 38	12 71	13 22	11 75	12 54
Fair result					
Longest		16 20	15 70		16 20
Shortest		3 99			3 99
Average		10 79			11 41
Dead					141 cases
Good result					
Longest	13 00	15 00	12 10		15 00
Shortest	43	26	82		26
Average	5 69	5 92	7 06		6 03
Fair result					
Longest		10 85			10 85
Shortest		2 78			2 78
Average		6 97			6 97
Poor result					
Longest		11 19	4 16	2 96	11 19
Shortest		15	25	05	05
Average		2 04	1 16	1 23	1 71

TABLE 5 3 —SQUAMOUS CELL EPITHELIOMA OF THE GENITOURINARY ORGANS

Postoperative Results According to Grade

	Grade I	Grade II	Grade III	Grade IV	All Grades
Information					408 (92 72% of 440)
Living	11 (55 55% of 20)	26 (26% of 100)	32 (17 77% of 180)	7 (6 48% of 108)	76 (18 62% of 408)
Good result	11 (100% of 11)	25 (96 15% of 26)	32 (100% of 32)	7 (100% of 7)	75 (20% of 375)
Fair result		1 (3 84% of 26)			
Dead	9 (45% of 20)	74 (74% of 100)	148 (82 22% of 180)	101 (93 51% of 108)	332 (81 37% of 408)
Good result	3 (42 85% of 7)	14 (23 72% of 59)	9 (6 38% of 141)	3 (3 26% of 92)	29 (7 73% of 375)
Fair result	1 (14 28% of 7)				
Poor result	3 (42 85% of 7)	45 (76 27% of 59)	132 (93 61% of 141)	89 (96 73% of 92)	269 (71 73% of 375)
Postoperative deaths	1	11	6	5	
Cause unknown	1	2	1		
Cause known but took place too early to consider		2		4	
Total good results	14 (77 77% of 18)	39 (45 88% of 85)	41 (23 69% of 173)	10 (10 10% of 99)	104 (27 73% of 375)
Total fair results	1 (5 55% of 18)	1 (1 17% of 85)			2 (53% of 375)
Total poor results	3 (16 66% of 18)	45 (52 94% of 85)	132 (76 30% of 173)	89 (89 89% of 99)	269 (71 73% of 375)

Duration of Postoperative Life According to Grade

	Grade I	Grade II	Grade III	Grade IV	All Grades
Information					408 cases
Living					76 cases
	Yrs	*Yrs*	*Yrs*	*Yrs*	*Yrs*
Good result					
Longest	18 47	19 06	21 06	13 82	21 06
Shortest	7 05	6 43	8 93	9 44	6 43
Average	12 21	12 69	13 13	10 48	12 63
Fair result					
Longest		12 48			
Dead					332 cases
Good result					
Longest	6 62	11 76	16 58	17 03	17 03
Shortest	4 86	1 16	1 93	4 93	1 16
Average	5 86	6 01	8 02	9 55	7 34
Fair result					
Longest	9 21				
Poor result					
Longest	2 87	12 22	10 68	4 80	12 22
Shortest	15	08	08	16	08
Average	1 86	2 23	1 56	1 20	1 55

TABLE 5 4.—EPITHELIOMA OF CAVITIES AND INTERNAL ORGANS OF HEAD AND NECK
Postoperative Results According to Grade

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*All Grades*
Information					233 (90 65% of 257)
Living	7 (58 33% of 12)	25 (22 52% of 111)	4 (4 49% of 89)	2 (9 52% of 21)	38 (16 30% of 233)
Good result	7 (100% of 7)	24 (96% of 25)	4 (100% of 4)	2 (100% of 2)	37 (16 81% of 220)
Fair result		1 (4% of 25)			1 (45% of 220)
Dead	5 (41 66% of 12)	86 (77 47% of 111)	85 (95 50% of 89)	19 (90 47% of 21)	195 (83 69% of 233)
Good result	3 (60% of 5)	10 (12 34% of 81)	3 (3 89% of 77)		16 (7 27% of 220)
Poor result	2 (40% of 5)	71 (87 65% of 81)	74 (96 10% of 77)	19 (100% of 19)	166 (75 45% of 220)
Postoperative deaths		4	8		
Cause unknown		1			
Total good result	10 (83 33% of 12)	34 (32 07% of 106)	7 (8 64% of 81)	2 (9 52% of 21)	53 (24 09% of 220)
Total fair result		1 (94% of 106)			1 (45% of 220)
Total poor result	2 (16 66% of 12)	71 (66 98% of 106)	74 (91 35% of 81)	19 (90 47% of 21)	166 (75 45% of 220)

Duration of Postoperative Life According to Grade

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*All Grades*
Information					233 cases
Living					38 cases
	Yrs	*Yrs*	*Yrs*	*Yrs*	*Yrs*
Good result					
Longest	19 40	15 15	14 13	16 32	19 40
Shortest	4 00	3 21	10 01	12 91	3 21
Average	11 29	10 98	12 10	14 61	11 36
Fair result					
Longest		12 79			12 79
Dead					195 cases
Good result					
Longest	5 53	12 00	13 79		13 79
Shortest	4 53	4 31	1 11		1 11
Average	5 18	8 22	7 02		7 43
Poor result					
Longest	9 75	9 00	6 62	2 63	9 75
Shortest	4 00	08	04	08	04
Average	6 87	1 28	79	82	1 09

TABLE 5 5 —CARCINOMA OF THE RECTUM

*Postoperative Results According to Grade**

	Grade I	Grade II	Grade III	Grade IV	All Grades
Information					587 (98 16% of 598)
Living	58 (56 31% of 103)	112 (38 22% of 293)	35 (25 17% of 139)	8 (15 38% of 52)	213 (36 28% of 587)
Good result	55 (94 82% of 58)	101 (90 17% of 112)	33 (94 28% of 35)	7 (87 50% of 8)	196 (92 01% of 213)
Poor result	3 (5 17% of 58)	11 (9 82% of 112)	2 (5 71% of 35)	1 (12 50% of 8)	17 (7 98% of 213)
Dead	45 (43 68% of 103)	181 (61 77% of 293)	104 (74 82% of 139)	45 (86 53% of 52)	375 (63 88% of 587)
Good result	4 (13 79% of 29)	13 (8 38% of 155)		2 (5 40% of 37)	19 (6 16% of 308)
Poor result	25 (86 20% of 29)	142 (91 61% of 155)	87 (100% of 87)	35 (94 59% of 37)	289 (93 83% of 308)
Total good results	59 (67 81% of 87)	114 (42 69% of 267)	33 (27 04% of 122)	9 (20% of 45)	215 (41 26% of 521)
Total poor results	28 (32 18% of 87)	153 (57 30% of 267)	89 (72 95% of 122)	36 (80% of 45)	306 (58 73% of 521)

Duration of Postoperative Life According to Grade

	Grade I	Grade II	Grade III	Grade IV	All Grades
Information					499 cases
Living					213 cases
	Yrs	*Yrs*	*Yrs*	*Yrs*	*Yrs*
Good result					
Longest	9 50	11 00	10 50	7 33	11 00
Shortest	1 33	1 20	1 33	4 00	1 20
Average	5 06	4 79	4 57	6 73	4 89
Poor result					
Longest	2 25	3 41	1 91	2 75	3 41
Shortest	1 37	1 16	1 41	2 75	1 16
Average	1 90	2 54	1 66	2 75	2 33
Dead					286 cases
Good result					
Longest	8 50	10 12		6 58	10 12
Shortest	1 83	1 17		4 00	1 17
Average	4 81	4 67		5 29	4 73
Poor result					
Longest	7 75	7 66	6 00	7 75	7 75
Shortest	0 41	0 50	0 08	0 12	08
Average	2 42	2 21	1 76	1 45	2 00

* This table does not include cases in [illegible] after operation or in the hospital or after the patient was dismissed if the interval after the [illegible] too short to determine whether or not the patient would have died from the carcinoma [illegible] in which the cause of subsequent death is unknown

TABLE

UNILATERAL

Percentage Survival Rates According to Involvement

Grade	*Axillary Metastasis*	*No Patients Operated on*	*No Patients Traced*	*Lived Three or More Years after Operation*		*Patients Operated on*
				No	*% of Those Traced*	
I	Present	10	10	10	100 0	10
	Absent	119	111	107	96 4	97
II	Present	183	178	121	68 0	177
	Absent	244	236	210	89 0	211
III	Present	782	770	385	50 0	743
	Absent	309	303	241	79 5	252
IV	Present	1520	1484	483	32 5	1362
	Absent	201	197	134	68 0	173

This table pertaining to cancer of the breast was recently published by Dr Harrington. It shows the influence of the grade of malignancy on metastasis and ultimate result.

The results which are on a three or more five or more, and ten or more year survival basis are not comparable to the results obtained in the other five groups of cancer (Tables 5 1 to 5 5 inclusive) which are on a good fair and poor basis however the following should be of interest as it shows a lower average grade of malignancy in cancers of patients who survived in contrast to a higher average grade of malignancy of cancers in patients who did not.

5 6

CARCINOMA OF BREAST*

of Lymph Nodes and Grades of Malignancy

Patients Traced	Lived Five or More Years after Operation		Patients Operated on	Patients Traced	Lived Ten or More Years after Operation	
	No	% of Those Traced			No	% of Those Traced
10	10	100 0	8	7	5	71 4
91	87	95 6	49	48	41	85 4
172	89	51 7	149	142	43	30 3
202	163	80 7	93	87	48	55 2
724	221	30 5	533	519	74	14 3
247	154	62 3	127	122	55	45 1
1334	281	21 1	945	921	110	11 9
168	96	57 1	115	112	44	39 3

The average grade of 1691 cancers in patients who lived three or more years after operation is 3 03 The average grade of 1101 cancers in patients who lived five or more years after operation is 2 93 The average grade of 490 cancers in patients who lived ten or more years after operation is 2 93 On the other hand the average grade of 1598 cancers in patients who failed to live three or more years after operation is 3 60 The average grade of 1847 cancers in patients who failed to live five or more years after operation is 3 53 The average grade of 1538 cancers in patients who failed to live ten or more years after operation is 3 47

TABLE 5 7 —PERCENTAGE OF THE FOUR GRADES OF CANCER IN VARIOUS SITUATIONS

Lip

	No	Per Cent
Grade I	85	15 82
Grade II	333	62 01
Grade III	113	21 04
Grade IV	6	1 11
Total	537	

Skin

	No	Per Cent
Grade I	21	8 20
Grade II	178	69 53
Grade III	44	17 18
Grade IV	13	5 07
Total	256	

Genitourinary Organs

	No	Per Cent
Grade I	24	5 07
Grade II	116	24 53
Grade III	206	43 53
Grade IV	127	26 84
Total	473	

Cavities and Organs of Head and Neck

	No	Per Cent
Grade I	16	4 41
Grade II	161	44 47
Grade III	145	40 05
Grade IV	40	11 04
Total	362	

Rectum

	No	Per Cent
Grade I	105	17 55
Grade II	299	50 00
Grade III	141	23 57
Grade IV	53	8 86
Total	598	

Breast

	No	Per Cent
Grade I	129	3 8
Grade II	427	12 7
Grade III	1091	32 4
Grade IV	1721	51 1
Total	3368	

TABLE 5 8 —PERCENTAGE OF METASTASIS OF CANCER IN RELATION TO GRADE

Organ	*Cases*	*Grade*	*Percentage*
Lip	67	I	00 00
	287	II	13 58
	92	III	68 47
	3	IV	100 00
Skin	2	I	00 00
	25	II	44 00
	16	III	75 00
	9	IV	100 00
Rectum	82	I	26 82
	290	II	44 13
	137	III	56 20
	51	IV	64 70
Breast	129	I	7 8
	427	II	42 9
	1091	III	71 7
	1721	IV	88 3

TABLE 5 9 —AVERAGE GRADE OF MALIGNANCY*

Cases	*Organ*	*Average Grade*
537	Lip	2 07
256	Skin	2 19
473	Genitourinary organs	2 92
362	Cavities and organs head and neck	2 57
598	Rectum	2 23
3368	Breast	3 30

Average grade of malignancy of cancer in various situations arrived at by adding the numerals indicative of the malignancy and dividing the result by the number of cases for example 1 plus 2 plus 3 plus 4 equals 10 divided by 4 equals 2 5 as the average grade for the four cancers or $\frac{1+2+\ +4}{4} =$

TABLE 5 10 —AVERAGE GRADE OF CANCER THAT METASTASIZED

Cases	*Organ*	*Average Grade*
105	Lip	2 65
32	Skin	2 93
260	Rectum	2 46
2495	Breast	3 52

TABLE 5 11 —AVERAGE GRADE OF CANCER THAT DID NOT METASTASIZE

Cases	*Organ*	*Average Grade*
344	Lip	1 88
20	Skin	2 10
300	Rectum	2 12
873	Breast	2 67

TABLE 5 12.—AVERAGE GRADE OF MALIGNANCY IN RELATION TO THE OBTAINED TOTAL RESULT

	Lip	
Total Result	*Cases*	*Average Grade*
Good	332	1 91
Fair	6	1 83
Poor	110	2 52
	Skin	
Total Result	*Cases*	*Average Grade*
Good	120	2 00
Fair	13	2 07
Poor	77	2 48
	Genitourinary Organs	
Total Result	*Cases*	*Average Grade*
Good	104	2 45
Fair	2	1 50
Poor	269	3 14
	Cavities and Organs of Head and Neck	
Total Result	*Cases*	*Average Grade*
Good	53	2 02
Fair	1	2 00
Poor	166	2 66
	Rectum	
Total Result	*Cases*	*Average Grade*
Good	215	1 96
Poor	306	2 43

CHAPTER 6

Biopsy in Tumor Diagnosis

John V Blady

INTRODUCTION

It is of historic interest that the biopsy procedure is less than one hundred years old Its first ardent advocate was Carl Ruge a gynecologist at the University of Berlin In 1878 he and his colleague Veit stated that the harmless excision of a piece of tissue from the portio vaginalis and examination of the excised tissue was the most important means of *recognizing malignant tumors* Most pathologists of that day ridiculed the idea Ruge and Veit persisted in their efforts and in 1899 Veit published his *Handbuch der Gynakologie* Frommel wrote the section on uterine cancer and stated that diagnosis of uterine cancer should always be based on the microscopic findings in a specimen of tissue obtained by biopsy or curettage

Until 1930 *prominent surgeons and pathol*ogists debated and scored each other in arguments on the advantages and the dangers of biopsy During this time many patients were treated for cancer without any confirmation of the clinical diagnosis In many others early cancers were allowed to become advanced and of quite obvious character because of the aversion or fear of some physicians to perform biopsies and their failure to recognize cancer

For the past two decades this procedure of removing a biopsy has been firmly established and unanimously accepted By biopsy is meant the removal of tissue from a lesion for microscopic examination by a pathologist The purpose of biopsy is to confirm a clinical opinion establish a definitive diagnosis and aid or guide in the decision as to treatment It may also give some idea as to the prognosis in a given case

Every lesion suspected of being cancer should be immediately biopsied All lesions that have persisted for ten days or longer and have increased in size should have a piece of tissue removed for microscopic study This may establish a diagnosis or may even detect an early cancer

The dangers inherent in obtaining a biopsy must not be overlooked neither must they be overemphasized In all cases the tumor or lesion should be handled as gently as possible In general one should avoid cutting through tumor tissue that is not located on any of the skin or mucous membrane surfaces and especially so if it is encapsulated It is preferable in such cases to excise the mass nodule or node

A biopsy should never be taken with dull *instruments The biopsy should be cleanly cut* in order to avoid unnecessary trauma of tissues thereby preventing the possible spread of cancer cells and also to avoid crushing and distorting cells in the specimen

A negative report on a biopsy must never be regarded as ruling out the existence of a malignant growth In the presence of a suspicious lesion the biopsy should always be re*peated*

METHODS OF OBTAINING A BIOPSY

The accepted methods by which tissue is obtained for histologic study are

1 by removal of a small piece of tissue with biting or cutting forceps
2 by incision and removal of a small piece or wedge of tissue with a scalpel
3 by excision or the complete removal of a lymph node or small tumor

ing may be readily controlled by pressure with either dry gauze or gauze saturated with hydrogen peroxide The application of a gelatin sponge (Gelfoam) to venous or small arterial bleeders will stop bleeding in a matter of minutes Bleeding may also be controlled by fulguration Where more persistent bleeding is encountered a deeply placed suture will compress or obliterate the opening in a vessel by contact with surrounding tissues

The selection of the site for the biopsy is important In Figure 6 3 the microscopic tissue section shows the transition from a hyperplasia of squamous cells to actual cancer This represents the ideal biopsy Tumor tissue that is grossly infected may be somewhat modified by the superimposed infection and a definite histologic diagnosis of cancer therefore may not be possible Superficially ulcerated lesions oftentimes are covered by granulation tissue and if care is not observed when the biopsy is taken the tumor may be missed and only chronic granulation tissue will be seen by the pathologist *A biopsy should always be taken from the region showing the least amount of infection and the wedge of tissue should be cut from growing tumor care being taken to cut deeply* A biopsy taken through the edge or periphery of a lesion as well as through a portion of the tumor may show the transition from normal to the abnormal

In taking the biopsy, the use of the scalpel (Bard Parker No 10 or 15) is preferred to the endothermic knife and loop Small fragments obtained with the cautery usually show complete destruction due to dehydration of the tissues There is definite shrinkage and distortion of cellular detail In taking the biopsy the operator must exercise care not to squeeze the small fragments of tissue Squeezing either with thumb forceps or after handling with dry gauze may alter the histologic structure and sometimes renders the tissue useless for study

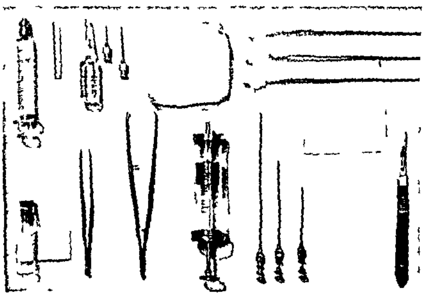


Fig 6-4 Paraphernalia used for the performance of an aspiration (needle) biopsy (Upper row) Five-cc procaine syringe file procaine hypodermic needles gauze cotton applicators (Lower row) Biopsy container smooth and sharp-toothed thumb forceps 20 cc aspirating syringe 18-gauge aspirating needle (1 1 5 or 2 inches in length) glass slides No 11 Bard Parker bistoury knife

3 *Excisional biopsy* finds its greatest use in the clinically significant lymphadenopathies especially where a primary lesion is not demonstrable The removal of a whole node is necessary

In performing an excisional biopsy care should be exercised in selecting a lymph node that would be representative of the disease in question *A safe rule is to select the node that has enlarged most recently or is hard and is suspicious of being part of the disease*

Small subcutaneous encapsulated tumors that are suspected to be cancer if not biopsied

by aspiration should be excised rather than incised for biopsy

Technic of excision The skin is prepared with a cleansing and sterilizing solution draped with sterile towels and a 1 or 2 per

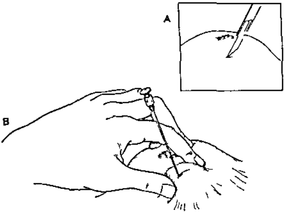


Fig 6 5 Technic of aspiration biopsy *A* After procaine has been injected the place of introduction of needle is incised with point of bistoury knife *B* An 18 gauge needle with stylet in place is inserted through the stab incision in the skin The point of the needle is guided into the tumor with the palpating hand The stylet is removed and a record syringe is then attached It is important to immobilize the mass to be aspirated between the fingers

cent solution of procaine hydrochloride is used to produce a field block around the area of the surgical field Small incisions are made for superficially situated nodes However for the excision of deep lying nodes an incision rendering adequate exposure is necessary The excision of the node is performed preferably by sharp scalpel dissection

4 *Needle aspiration biopsy* has been popularized by Martin and Ellis [30] It can be easily and quickly performed in routine office practice

Its use is indicated in any case of a suspected malignant tumor in which the lesion lies below the surface of normal tissue Innumerable successful aspiration biopsies have been performed on lesions of the antrum nonulcerated lesions of the oral cavity parotid and submaxillary glands breast lungs mediastinum liver bones prostate and regional lymphadenopathies (cervical axillary and inguinal) of unknown nature

The paraphernalia required for aspiration biopsy are (1) 20 cc record syringe (2) 18 gauge needle (the length of the needle will depend on the depth of the tumor, for subcutaneous masses a 5 cm needle is usually employed whereas for lung biopsy a 10 to 15 cm needle will be required) (3) bistoury knife (No 11 Bard Parker blade), (4) procaine needle and syringe (5) container for tissue and (6) normal saline or formal alcohol solution (Figure 6 4) Silverman and Franseen have devised modifications of the needle used for the aspiration in an effort to improve the chance of obtaining tissue

The technic of aspiration biopsy as published by Martin and Ellis [30] is summarized in the captions of Figures 6 4 6 5 6 6 6 7,

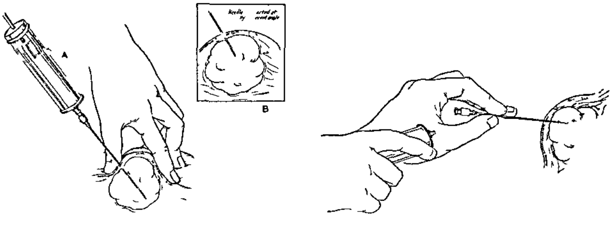


Fig 6 6 Aspiration biopsy (*Left*) A Full suction is applied to syringe and the needle is advanced a distance of 1 to 1 5 cm depending on size of tumor B While vacuum is maintained the needle is withdrawn and reintroduced into the mass from a slightly different angle At the same time the needle is rotated so as to loosen tissue and facilitate its aspiration into the needle Repeat maneuver two or three times (*Right*) The suction is carefully and slowly released the syringe disconnected and the needle removed from the tissues

and 6 8 In order to utilize this procedure satisfactorily however it is required that the pathologist have adequate experience in the interpretation of stained sections of small biopsies and especially if fixed stained smears

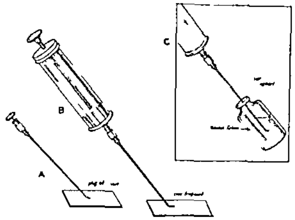


Fig 6 7 Aspiration biopsy The stylet is inserted into the needle and the plug or core of tissue expelled on slide (A) or into fixing fluid (C) The syringe is then attached to the needle and air is blown through the needle by forceful pressure on the plunger of the syringe (B) This maneuver may expel small fragments of tissue adherent in the lumen of the needle

are used Stewart [31 49] has described the histology of fixed stained smears of tissues obtained by aspiration (Figure 6 9)

The limitations of aspiration biopsy are well illustrated in Figures 6 10 6 11, and 6 12 A negative aspiration biopsy does not mean the absence of cancer but merely informs us that in the specimen obtained cancer was not present

In the punch method of biopsy a large trocar is inserted into the tissue in a manner similar to the introduction of a needle and a plug of tissue is cut out and withdrawn by means of a hooked obturator [23] The tissue thus obtained is treated in the same manner as that obtained by the aspiration needle method

5 *Curettage* is employed in obtaining tissue from such structures as bones uterus draining sinuses and ulcers In bone lesions (cysts chondromas and giant cell tumors) the bone is exposed and the tumor is thoroughly curetted These curettings serve as satisfactory tissue for microscopic examination In cancer of the body of the uterus the diagnostic curettage is the method of positive diagnosis Draining sinuses and ulcers may be curetted and the tissue rendered for histologic study When biopsy by incision or biting forceps is not feasible it may be possible to obtain tissue by curettage

6 *The aspiration of secretions from body cavities* is being accorded ever increasing recognition Specimens are obtained either by paracentesis or by aspiration of body secretions as originally advocated by Papanicolaou [38] and the diagnosis is established on evaluation of the cellular structure

Paracentesis not infrequently yields tissue for histologic study The sediment that is ob

Fig 6-8 Section of plug of tissue from an aspiration biopsy of the third cervical vertebra under fluoroscopic guidance Slide shows metastatic squamous-cell carcinoma Primary tumor was located in the piriform sinus

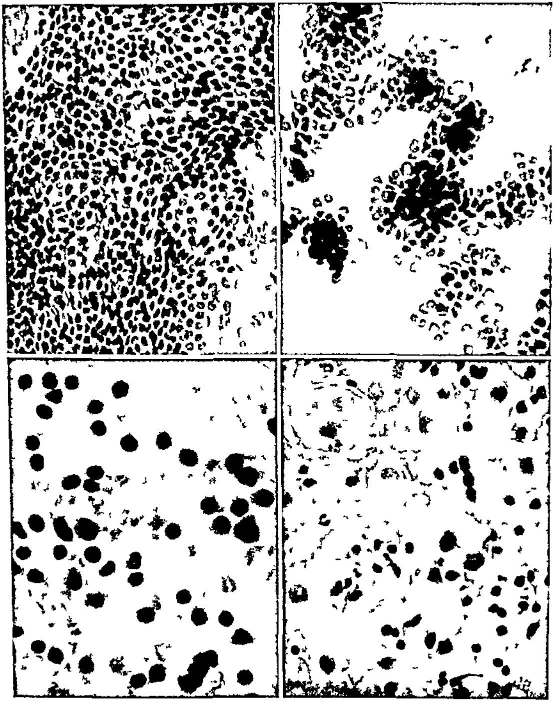


Fig 6-9 Stained smears of aspirated material (*Upper left*) Fibroadenoma of breast cells small regular coherent (*Upper right*) Carcinoma of breast cells hyperchromatic and loose (*Lower left*) Plasma-cell myeloma (*Lower right*) Gaucher's splenomegaly (*From* H E Martin and E B Ellis Aspiration Biopsy chap 6 (in Treatment of Cancer and Allied Diseases G T Pack and E M Livingston (eds) 1st ed., New York Paul B Hoeber Inc 1940)

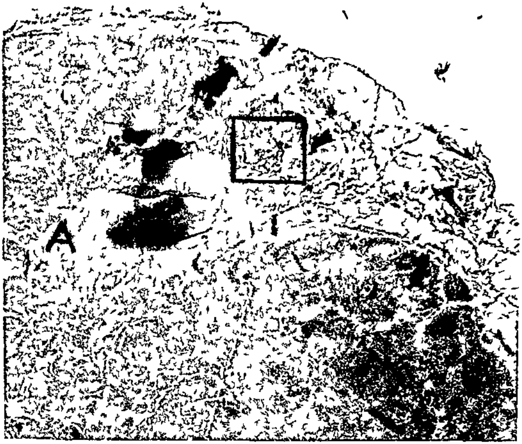


Fig 6 10 One of the limitations of aspirat on biopsy is well illustrated in this low power project on of a section through a lymph node showing *A* area of trauma and hemorrhage along the needle tract and rectangular area showing metastases which is enlarged in Figure 6-11

F g 6-11 These small nests of cancer cells are the only foci of metastases a d occur in only one section of the lymph node shown in F gure 6-10 In the presence of such minute metastases th chances are infinitesimal *indeed of i troducing the needle into the involved portion of the lymph* node a d aspirati g the few nests of neoplast c cells shown above

tained from ascitic fluid should be centrifuged and subjected to fixation

The cytologic study of smears of secretions obtained from lungs vagina uterus bladder and stomach may lead to the detection of early cancer of any of these regions It finds its greatest usefulness in the field of cancer detection as a screening method

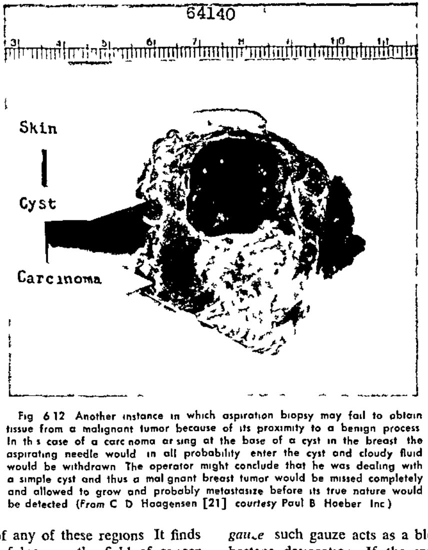


Fig 6 12 Another instance in which aspiration biopsy may fail to obtain tissue from a malignant tumor because of its proximity to a benign process In this case of a carcinoma arising at the base of a cyst in the breast the aspirating needle would in all probability enter the cyst and cloudy fluid would be withdrawn The operator might conclude that he was dealing with a simple cyst and thus a malignant breast tumor would be missed completely and allowed to grow and probably metastasize before its true nature would be detected (From C D Haagensen [21] courtesy Paul B Hoeber Inc)

THE HANDLING AND PRESERVATION OF BIOPSY TISSUE

The proper handling of biopsy material is just as important as its removal If the laboratory is near so that the tissue may reach its destination within an hour it is advisable to deliver the tissue to the pathologist in the fresh state Small pieces of tissue if exposed to the air will dry in 30 minutes or less and while such partially desiccated specimens frequently are not completely unfit for microscopic diagnosis they present changes in nuclear detail that are confusing and may lead to an error in diagnosis The best method is to place the biopsy specimen in a 10 to 20 cc tightly stoppered wide mouth bottle Fresh tissue should never be wrapped in *dry gauze* such gauze acts as a blotter that only hastens desiccation If the interim between offices and laboratory is to be several hours and no fixative is at hand the specimen should be placed in a large bottle with a gauze sponge moistened in saline solution and then stoppered

Along with the specimen the pathologist should be given pertinent data such as (1) the source of the tissue (2) the age of the patient (3) a brief history and (4) the clinical nature of the lesion Breast biopsies and endometrial curettings should be accompanied by a resume of the menstrual cycle

There are many types of fixatives but most of the good standard solutions are designed

as the first step in special handling that is special staining For this reason the selection of the fixative should be left to the pathologist who is to read the slides

If a fixative must be used the safest for routine procedures is a 4 per cent to 10 per cent solution of commercial formaldehyde A layer of marble chips should be kept in the bottom of the stock bottle of formaldehyde to prevent its becoming acid The time of preparation of sections from formalin fixed tissue is usually about five days This time may be shortened to two days by the use of a combined fixing and dehydrating agent The best of these is formal alcohol With the use of this solution and an automatic tissue changer, sections may be prepared in 24 hours but it is difficult to avoid some shrinkage with this method

Biopsy material such as scrapings and needle biopsies in which the individual pieces are too small to handle singly should be treated like an aspirated fluid The curette is washed off or the needle rinsed in a small amount of normal saline and the whole solution containing the small fragments is sent to the laboratory Cells should not remain in the saline solution for longer than six hours because they are apt to undergo nuclear changes that make diagnosis hazardous In the laboratory the solution is centrifuged and the button of sediment which is big enough to handle as a biopsy specimen is treated as such The addition of a few drops of blood serum to the initial solution results in coagulating the protein and enmeshing the cells to hold them together and give the specimen body [26] If a fixative is used Helly s solution is probably the best since it seems to preserve the finer details of cell structure although formalin or formal alcohol seems to give as good results With the latter fixatives the mounted specimen is made available for study 12 to 24 hours earlier than with Helly s solution

The rapid method of treating material obtained by needle biopsy permits immediate preparation for microscopic study [31 49] The tissue fragments are placed on a glass slide and smeared by pressure applied by means of another slide The resulting smear is dried in air fixed by heat and stained in the routine method This is a crude method and usually only the obvious cancer may be diagnosed with certainty, although the pathologist experienced in the interpretation of such smears can quickly and readily determine whether the lesion is benign or malignant (Figure 6 9)

Frozen section is a helpful procedure in the histologic diagnosis of a great many lesions treated surgically and suspected of being cancerous It is especially useful in the surgical treatment of tumors of the breast By this method no time is lost in the initial treatment of cancer The report of the pathologist may be obtained within a matter of 15 to 20 minutes and the proper therapeutic procedure may then be carried out immediately In some instances of unusual histology the frozen section method may not be satisfactory and it is then necessary to await a histologic diagnosis on the routine paraffin section

CHOICE OF BIOPSY METHODS FOR VARIOUS ANATOMIC REGIONS

SKIN

Suspected intact lesions are best biopsied with the scalpel while the biting or cutting forceps is especially useful for biopsy of proliferative growths and for some ulcerating lesions (Figure 6 13) Moles and other benign growths in which cancer is not suspected should be excised in toto with a generous margin of skin around the entire lesion

Any growth that is even remotely suspected of being melanoma should always be widely excised Every pigmented mole should be microscopically studied The pathologist when studying moles especially in children must have clinical facts to aid him

LIP

For the small superficially ulcerated or nodular tumors incisional biopsy is the method of choice When the tumor is a large proliferative lesion tissue may be obtained with the biting forceps

NASAL CAVITY AND NASOPHARYNX

Biopsies of the nasal cavity and nasopharynx are readily obtained by means of a biting or cutting type of forceps (Figure 6 14) In the

nasopharynx it is necessary to have either direct visualization of the tumor, or palpatory aid during the biopsy procedure With the basket or cup type of forceps introduced through either one of the nasal cavities and

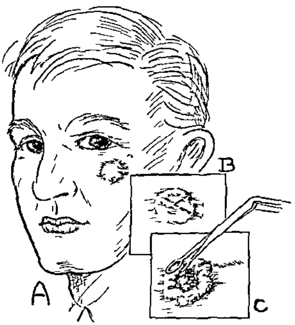


Fig 6-13 Methods of biopsy in skin lesions A and B indicate outline of wedge to be removed as biopsy and which includes normal as well as neoplastic tissue (see Figure 6 3 upper) C Method of taking a biopsy with cutting or biting forceps (see Figure 6 3 *lower*)

with the mirror in the oropharynx visualization of the region may be had (Figure 6 14A) The curved type of biting forceps which can be used with the universal handle has the advantage of introduction through the mouth into the nasopharynx and here again tissue may be obtained by mirror vision in the oropharynx The direct vision obtained with the nasopharyngoscope in a great many instances is of considerable help When these methods fail the nasopharyngeal lesion is identified with the index finger which is introduced through the mouth into the nasopharynx and is used as a guide for the forceps (Figures 6 14B 6 14C) The latter may be introduced either through the nasal cavity or when the curved forceps is used it may be introduced through the mouth along the guiding finger In a suspected nasopharyngeal fibroma or angiofibroma biopsy should be done cautiously since this type of tumor is usually highly vascular and serious hemorrhage may result

It is desirable to have these patients hospitalized for this biopsy procedure

It is well to remember that *a negative biopsy does not mean the absence of cancer* This is especially well demonstrated in the

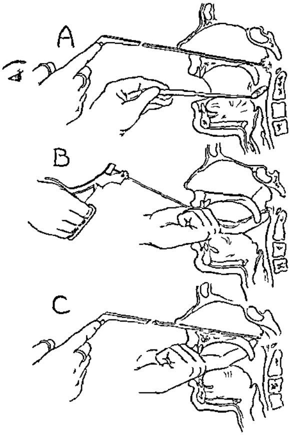


Fig 6-14 A biopsy from the nasopharynx may be obtained by any of the three methods illustrated above A Biopsy forceps introduced through the nasal cavity into the nasopharynx With the mirror in the oropharynx the tumor is seen and the biopsy is accurately taken B With the universal curved cannula biopsy forceps introduced through the mouth a biopsy is taken from the mass in the nasopharynx with the aid of the palpating finger C By identifying the nasopharyngeal mass with the finger the biopsy may be obtained with a forceps introduced through the nasal cavity (Courtesy Hayes E Martin Cancer of the Head and Neck *J A M A 137* August 7 and 14 1948)

case of lymphoepithelioma of the nasopharynx This tumor is characteristically small and sometimes scarcely visible on nasopharyngoscopy or posterior mirror rhinoscopy Several repeat biopsies may be required before a positive diagnosis is obtained

ORAL CAVITY

Oral cavity includes the anatomic regions of the tongue buccal mucous mem

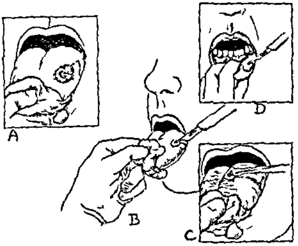


Fig 6 15 Methods of taking biopsy from lesions on lip and tongue with cutting forceps or by incisional biopsy

PARANASAL SINUSES

The paranasal sinuses include the antrum and the ethmoid frontal and sphenoid sinuses When a tumor arising in any of these regions has perforated the confines of the bony wall a biopsy with the biting forceps is readily obtained However in the absence of visible tissue for biopsy other diagnostic procedures are required The maxillary antrum and the frontal and ethmoid sinuses may be explored and biopsied by means of the aspirating needle (Figure 6 16) Watson reported success in 39 instances of paranasal sinus cancer and failure in four patients When aspiration biopsy fails a Caldwell Luc or other type of exposure should be employed

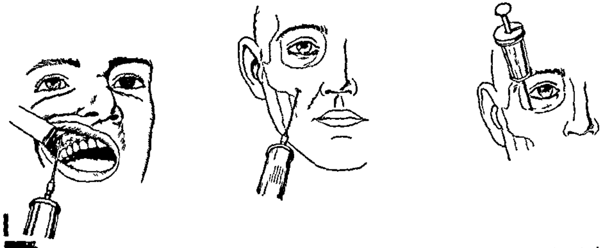


Fig 6 16 Methods of performing an aspiration biopsy on the maxillary antrum (*Left*) Approach through the gingival buccal gutter at the first molar level *This is especially suitable for tumors situated in the anteroinferior* portion of the antrum (*Middle*) Anterior approach through *the skin of the cheek for cancers involving the supero-*anterior portion of the antrum (Right) The floor of the orbit approach is *especially suitable for tumors perforating* into the orbit (From W L Watson [54] courtesy Laryngoscope)

brane gingiva, tonsil and oropharyngeal wall There are a number of noncancerous processes such as syphilis and tuberculosis that may be confused with cancer

From a fungating tumor a tissue specimen may be obtained with biting forceps In a deeply infiltrating lesion the scalpel should be used (Figure 6 15)

Biopsy tissue may be readily obtained from lesions at the base of the tongue with curved biting forceps guided either by direct vision in a laryngeal mirror or by palpation of the tumor with a finger (Figure 6-17) Occasionally direct laryngoscopy is necessary for proper exposure

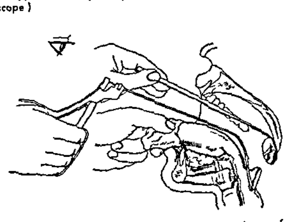


Fig 6 17 Removal of biopsy specimen from lesion of extrinsic larynx or hypopharynx with *curved biopsy forceps guided by a mirror (From Hayes E Martin* Cancer of the Larynx chap 5 in Loose *Leaf Surgery* *Baltimore* Williams and Wilkins Company)

For neoplastic lesions of the sphenoid that have not eroded through the sinus wall trephination of the sinus for exploration and biopsy is the indicated procedure

LARYNX AND HYPOPHARYNX

The diagnosis of cancer of the larynx should always be confirmed histologically Biopsy of lesions in the larynx the subglottic area the piriform sinuses and hypopharynx necessitate the aid of direct laryngoscopy Tissue may be obtained in certain instances by the use of a laryngeal mirror guiding a curved biopsy forceps in some lesions on the epiglottis aryepiglottic folds vallecula and lateral pharyngeal walls (Figure 6 17)

SALIVARY GLANDS

Aspiration biopsy will frequently establish the diagnosis Incisional biopsy is contraindicated except for frozen section study in which case the surgeon should be prepared to carry out the necessary therapeutic procedure immediately

THYROID GLAND

Thyroid cancer is not uncommon Cole and associates state a large percentage of asymptomatic thyroids will reveal carcinoma in its early stage In our series the diagnosis was made only in the surgical laboratory in 58 per cent of cases in 21 per cent it was first made in the operating room and in another 21 per cent it was made clinically before therapy

It is desirable therefore to obtain a preoperative diagnosis in diseases of the thyroid whenever possible Watson and Pool reported 74 *aspirations* performed on the thyroid gland of which 62 were positive for cancer and 12 were negative

Frozen section study of thyroid tissue at operation is not always reliable When dealing with solitary nodules the entire mass should be removed and if found adherent to surrounding tissue a partial thyroidectomy (lobectomy) should be carried out A frozen section study may help to detect cancer If the microscopic diagnosis is positive proper cancer therapy should be immediately instituted

NECK

Aspiration biopsy of a lump in the neck is the most efficient and the quickest method of confirming or establishing a diagnosis *Most persistent cervical adenopathies in the adult are malignant metastases from intraoral or pharyngeal cancer* In our experience aspiration biopsy of cervical lymph nodes has been diagnostic in 85 per cent of the cases

In the malignant lymphomas aspiration biopsy may be diagnostic Frequently however the pathologist is unable to make a diagnosis and subsequent excision of a node is necessary When malignant lymphoma is suspected a surgical excision of a lymph node should be the immediate decision rather than aspiration biopsy When several enlarged nodes are present it may be helpful to the pathologist if a small node is submitted along with a large one The small node may show the initial process without secondary infection or necrosis that so often is seen in large lymph nodes

BRONCHI AND LUNGS

Tissue from lesions in the bronchi and lungs may be obtained by (1) bronchoscopic biopsy (2) aspiration (needle) biopsy (3) tissue that may be coughed up or expectorated by the patient (4) exploratory thoracotomy (5) aspiration of exfoliated cells that may be found in bronchial secretions or pleural fluid and (6) examination of sputum

Bronchoscopy is the greatest single aid but because some tumors may be located in inaccessible regions the bronchoscope has its limitations The main or primary bronchus is the site of the primary growth in about 80 per cent of all cases According to Norris in a series of 310 cases of proved cancer of the lung the right upper lobe was involved in 63 cases and the left upper lobe in 40 cases Positive bronchoscopic biopsy was obtained in 37 of the 63 cases (58 7 per cent) involving the right upper lobe and only in 13 cases (32 6 per cent) of the 40 involving the left upper lobe Of the seven lesions located in the right middle lobe four positive biopsies were obtained (57 0 per cent) On the other hand of 61 lesions located in the stem or main bronchi on either side positive biopsy was obtained

in all cases of 70 cases with lesions in the right lower lobe 62 positive biopsies (88 6 per cent) were obtained of 44 cases with lesions in the left lower lobe 38 positive biopsies (86 4 per cent) were obtained An analysis of

Fig 6 18 The spherical mass in the left upper lobe was aspirated under roentgenoscopic guidance and sections of the aspirated material were reported as carcinoma Bronchoscopy did not reveal any tissue from which a specimen could be obtained

the method of biopsy in these cases revealed the following

		Cases	Per Cent
1	By bronchoscopic biopsy	221	71 3
2	By aspiration biopsy	45	14 5
3	From study of pleural fluid	12	3 9
4	Lymph node biopsy	12	3 9
5	Cytologic study of sputum	2	0 6
6	Exploratory thoracotomy	9	2 9
7	Biopsy through the thoracoscope	1	0 3
8	Autopsy	8	2 7

Aspiration Biopsy of Lung Tumor

For the lesions that are inaccessible to bronchoscopic biopsy aspiration biopsy has been used successfully only in those cases in which other methods have failed At Temple University Hospital 217 needle biopsies were performed on lesions in the lung between 1936 and 1947 [41] A positive diagnosis of pulmonary carcinoma was obtained by aspiration biopsy in 135 cases (61 per cent) Some thoracic surgeons, namely Ochsner Holman and Overholt, have voiced strong opposition to the use of aspiration biopsy in lung lesions This opposition is based primarily on the contention that the needle biopsy procedure may spread tumor along the needle tract We have never observed this complication Rosemond and his associates report that of 19 patients in whom a needle biopsy was done for cancer of the lung 8 are still living from one to five years after operation without evidence of residual recurrent or metastatic tumor and eleven patients who died revealed no evidence of any spread along the needle tract

For aspiration biopsy of a lung lesion the patient is placed in a horizontal position The site for the introduction of the needle is carefully selected after roentgenographic and roentgenoscopic study Sometimes a deep seated lesion is equidistant from all the nearest skin surfaces as for example in hilar tumors in which case one approach may be preferred because of less danger of injury to important adjacent structures In such a case the roentgenoscope is particularly useful in selecting the safest avenue of approach (Figure 6-22) The center of the mass is then localized on the

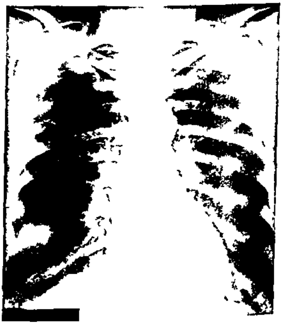


Fig 6-19 Circumscribed peripheral carcinoma of the lung diagnosed by needle biopsy (From G P Rosemond W E Burnett J H Hall [41] courtesy Radiology)

skin surface The skin is prepared with a suitable disinfectant and 1 per cent procaine is injected into the skin subcutaneous tissues and pleura The position of the needle and tumor are carefully checked roentgenoscopically in the lateral and anteroposterior or posteroanterior positions and if the needle is found to be in line with the lesion it is advanced into the substance of the tumor

Fig 6 20 Mass in left hilar region The inset is the bronchogram of the left bronchus demonstrating the displacement of the upper lobe bronchus and irregularity in its outline Bronchoscopy was performed and displacement was noted but no tumor tissue was obtained The mass was then aspirated under fluoroscopic guidance and the aspirated material was reported as carcinoma (*From J V Blady [6] courtesy American Journal of Roentgenology Radium Therapy and Nuclear Medicine*)

Expectorated Material

Not infrequently patients with cancer of the lung may expectorate solid pieces of tissue We have observed this on several occasions The coughed up specimen is treated as a biopsy specimen and is prepared for study in the usual manner

Sputum may be examined for cells that may have been shed from the surface of the bronchi Pleural fluid may also be studied for cancer cells The cytologic study of pleural fluid by the cell block technic will reveal tumor cells in about three fourths of the patients with carcinoma involving the pleura

Exploratory Thoracotomy

Exploratory thoracotomy should be performed with dispatch when a diagnosis cannot be made by other methods

ESOPHAGUS

The esophageal tube can be visually studied with the esophagoscope through which a biopsy specimen can be obtained

STOMACH

A biopsy in cancer of the stomach is rarely possible Tissues may be obtained through the open end gastroscope with long biting forceps In all cases where there is clinical roentgenologic and/or gastroscopic evidence of a lesion in the stomach an exploration is urgent

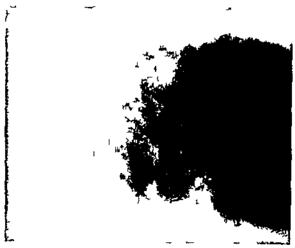


Fig 6 21 This small spherical tumor was found in the posterior portion of the lung on a routine examination in a Cavalry officer Various clinical diagnoses such as Glander s disease cancer and chondroma were proposed Because so much interest was aroused the officer became worried and wanted the diagnosis settled Under fluoroscopic guidance a successful aspiration biopsy was done The above roentgenogram shows the needle just piercing the mass The tissue obtained showed normal cartilage

INTESTINE

For lesions of the small intestine surgical exploration with resection of the lesion is indicated The exact histologic nature is determined after surgery

Lesions of the colon except for the sigmoid portion must be explored Sigmoidoscopic examination is not difficult Specimens are taken with the sigmoid biopsy forceps Care should be observed that part of the base of the lesion is included in the specimen It is recommended that a total excision of all polypoid growth be made for histologic study Such a biopsy requires a surgical procedure whereby the bowel is explored through a perineal approach and the lesion is completely removed If this polyp is proved to be benign on histologic examination the procedure is curative if on the other hand it is a malignant tumor then further radical surgical procedures are indicated

RECTUM

All rectal lesions should be biopsied All polypoid growths should have specimens taken from the base as well as from the polyp These biopsies are best taken with biting cup forceps

ANUS

Biopsy specimens may be taken with the biting forceps or by the incisional method from lesions of the anus If a melanoma is suspected the lesion should be removed by wide surgical excision under general anesthesia

LIVER

The liver may be studied histologically by means of a wedge biopsy at the time of abdominal exploration or by needle aspiration In recent years needle biopsy has become increasingly popular for the histologic examination of liver tissue

The indications for needle biopsy of the liver are

1 Any problem of liver dysfunction
2 Hepatomegaly of undetermined origin
3 Primary or metastatic neoplasm of the liver
4 Hepatic cirrhosis
5 Unrecognized systemic diseases of the liver

The site of biopsy is determined by the physical conditions found on examination If the liver is enlarged the needle may be inserted through the abdominal wall Care should be observed that the puncture is made at least about 5 cm from the palpable edge of the liver This may obviate perforation of abdominal viscera By pointing the needle obliquely toward the head of the patient the danger of visceral perforation is minimized

A small liver is approached transpleurally in the right anterior or midaxillary line For this approach the liver dullness should be marked out during ordinary respiration either in the anterior or midaxillary lines

The aspiration needle is inserted through a small incision and the patient is asked to inhale and exhale deeply two or three times He is instructed to hold his breath at the end of expiration and the needle is then inserted a distance of approximately 6 cm through the

chest wall (2 to 3 cm into the substance of the liver) and the biopsy is aspirated in the usual manner If tissue is not obtained the procedure is immediately repeated until definite tissue is obtained

will occasionally render a diagnosis arousing suspicion of a malignant tumor Kidney tumors are often diagnosed on clinical and roentgen findings Exploration is necessary and if a tumor is found the kidney is removed

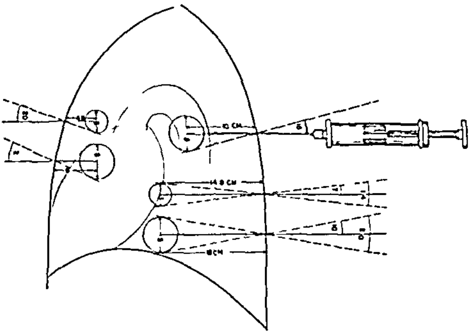


Fig 6 22 This schematic diagram of the lateral chest indicates some of the difficulties of performing an aspiration biopsy on small and deep-seated lesions A cm mass situated at 6 cm from the skin surface has a permissible angle of deviation of 24 ; at 10 cm 15 ; and at 15 cm only 10 This presupposes that the exact center of the tumor is carefully projected and localized on the skin surface It is only rarely possible however to localize the exact center of a tumor mass on the skin surface and even then any slight accidental moving of the patient will change the center on the skin surface A mass 3 cm in diameter has an angle of deviation of only 9 at 10 cm and only 6 at 15 cm This readily explains how easily either a small mass or one located at more than 10 cm from the surface may be missed by the aspirating needle unless the procedure is performed with fluoroscopic aid (From J V Blady [6] courtesy American Journal of Roentgenology Radium Therapy and Nuclear Medicine)

Complications following aspiration biopsy may be minimal if there is proper selection of the patient and prebiopsy estimation of prothrombin time Safdi and co-workers [43] were successful in demonstrating neoplastic tissue in 41 of 53 patients

PANCREAS

Differentiation between pancreatitis and cancer is difficult

KIDNEY

Biopsy plays an unimportant part in the diagnosis of diseases of the kidneys Cytologic study of the urine sediment or of aspirated secretions from the kidney pelvis and ureter

Frozen section study is rarely done A Wilms's tumor should not be biopsied

BLADDER

Cystoscopic examination of the bladder is most important A biopsy can be taken readily with special forceps through the cystoscope Papillary tumors that may appear benign should be biopsied before they are treated by fulguration Many so-called benign papillomas of the bladder treated without benefit of a biopsy later are shown to recur and are diagnosed on biopsy as a malignant papilloma or a frank carcinoma

If satisfactory tissue cannot be obtained through the cystoscope suprapubic explora

tion is justifiable for biopsy purposes and treatment

PROSTATE

Because of its position, biopsy of the prostate gland may be done by needle aspiration transurethral resection, or surgical exploration

Needle aspiration has many advocates In the large inoperable prostatic cancers aspiration biopsy is a simple and important procedure as it substantiates the clinical diagnosis of cancer and justifies the use of proper therapeutic measures Goller devised a needle with a small cutting screw on its point Ferguson used a special 18 gauge needle the Hoffman punch has been used for this purpose [24]

The procedure of aspiration biopsy of the prostate is as follows The needle with the obturator in place is inserted through the prepared skin With the finger in the rectum the needle is guided into the region of the prostate to be biopsied The obturator is removed and the aspirating syringe is attached for the aspiration

Transurethral resection is indicated if there is urinary obstruction associated with prostatic disease Tissue obtained by this means if not so small as to be affected by the heat, may be adequate for diagnostic study Suspected regions within the prostate may be biopsied by this method if while doing the resection an examining finger is inserted into the rectum to direct the loop to the focus in question

TESTIS

Patients thought to have neoplasms of the testicle are admitted to the hospital immediately for orchiectomy Surgical or aspiration biopsy procedures are not advised If cystic tumors are found an aspiration may be performed

PENIS

The diagnosis of a penile cancer is established by incisional biopsy If phimosis is present a dorsal slit or circumcision may be necessary to expose the lesion

UTERINE CERVIX

Any area that bleeds after a pelvic examination or after sponging of the surface of the cervix with cotton should be biopsied

The squamous margin of the squamocolumnar junction is the point of origin of the common squamous cervical cancer In an effort to afford a thorough examination of this region, circular biopsies have been employed Scheffey advocated the use of a cold knife in doing the circular or cone biopsy Ayer devised a surgical cone knife for this purpose By this means the removed collar of tissue could be examined by multiple biopsies or by embedding the entire collar of tissue in paraffin and doing a serial section study

Gusberg devised a special cone curet which permits the circumferential removal of a specimen The procedure of obtaining the specimen by this means is simple The cervix is steadied with the tenaculum and the snugly fitting cone curet is pushed into the canal about 1 cm beyond the external os The cutting cups are closed with a rapid slightly twisting motion This removes a circumferential piece of tissue that includes the squamocolumnar junction By means of this curet 500 women over 35 years of age who had no symptoms or lesions suggesting uterine cancer were examined by Gusberg Intraepithelial carcinoma was discovered in 10 cases and basal cell hyperplasia in 10 other cases

Foote and Stewart [19] have demonstrated that if biopsies are taken from 12 3 6 and 9 o clock positions the possibility of missing an in situ carcinoma is reduced to a minimum Each specimen is placed in a separate tube and labeled to indicate its site Beecham and Emich [5] have followed this method In 2 145 cervical biopsies from January 1 1946 through September 1 1951 invasive cancer was found in 107 cases and noninvasive cancer in 21 cases As it would be physically impossible to biopsy all cases seen in a clinic they use the following criteria to aid them in selecting the cases for biopsy (1) any lesion that demonstrates the slightest bleeding on sponging with cotton at any age level (3) all cervical lesions in women over 35 years of age before treatment is instituted (3) all cervical lesions that arouse suspicion in the examiner s mind even though there are no signs of traumatic bleeding

The true value of smear diagnosis in the

[illegible]

[illegible]

UTERUS

In cancer of the endometrium [illegible] biopsy is still the only decisive diagnostic procedure. For a comprehensive discussion of cytologic diagnosis, the reader is referred to Chapter [illegible] by Papanicolaou and Foot.

BREAST

A biopsy of a breast tumor may be performed by the following methods: (1) wedge biopsy and immediate frozen section examination, (2) excision of the whole tumor and immediate frozen section, and (3) aspiration. Haagensen [21] advocates the following method:

> We cut down directly upon the tumor and excise a small wedge. The whole tumor is not excised unless it is very small, that is, less than 2 cm in diameter, or unless, as the dissection develops, it is obviously seen to be a cyst or a fibroadenoma. If frozen section shows carcinoma, radical mastectomy is performed. If, as is sometimes the case, the first specimen fails to yield a diagnosis, another is removed. If the pathologist is still unable to make a diagnosis after studying several specimens, he asks the surgeon to close the wound and wait 24 hours for an opinion based on permanent sections.

In many clinics the entire tumor is removed as a local excision and sent to the laboratory for frozen section study. While waiting for the report the wound is carefully closed. If the report is a benign tumor the operation is concluded. If, on the other hand, a cancer is diagnosed, the patient is completely redraped, the used instruments are discarded, and the operating team regowns and regloves before commencing a radical mastectomy.

Aspiration biopsy has been advocated by some and especially the Memorial Hospital Group. Others have advanced criticisms because of possible failures in obtaining representative tissue by this method. In our experience aspiration biopsy of [illegible] can [illegible]

[illegible]

BONE

[illegible] a complete examination [illegible] which should be the [illegible] of the surgeon who is prepared to carry out the treatment. Ill advised and improperly performed biopsy may, and frequently does, reduce the patient's chance of cure to zero.

The biopsy of bone may be either surgical or aspiration. The surgical biopsy should always be regarded as an operation of major importance and should be performed by the surgeon who is to carry out the later treatment. To the pathologist the biopsy may not be diagnostic without clinical data, laboratory and chemical studies, and a thorough roentgenographic examination. It is imperative, therefore, that these studies be completed and that the biopsy be the last and completing procedure in establishing the diagnosis.

Aspiration biopsy is adaptable to all types of bone tumors except those in which the tumor is deeply situated and surrounded by a zone of normal bone through which the needle cannot be made to penetrate.

For the aspiration of bone tumors not readily localized by ordinary physical examination, the site of intended puncture and proper direction of the needle are determined by careful roentgenographic and roentgenoscopic study. In regions such as the head or neck of the femur, the pedicle or portion of a body of a vertebra, aspiration biopsy under roentgenoscopic guidance is a safe and exact procedure. It may be advantageous in most cases to elect the site for the introduction of the needle into the tumor where the bone shows evidence of destruction or of fracture, as this site will permit the needle to be introduced into the tumor itself without undue difficulty. This was well demonstrated in one of our cases of [illegible] in the neck of the femur, which showed an area of radiolucency in the cortex [16]. The [illegible] needle was inserted through the [illegible] part of the thigh above

the greater trochanter By adducting the leg medially the lesion was satisfactorily exposed and after ascertaining roentgenoscopically that the needle was in the lesion the aspiration was performed A diagnosis of osteogenic sarcoma was obtained on this smear

Fig 6-23 Tissue obtained on aspiration of a cystic tumor of the pubis was reported as fibrosing giant-cell tumor

Snyder and Coley reported a series of 568 aspirations in 474 individuals There were no immediate complications, no late sequelae nor any evidence to suggest that this diagnostic procedure had encouraged the development of metastasis Such various tumors as osteogenic sarcoma endothelioma (Ewing s sarcoma) reticulum cell sarcoma of bone giant cell tumor metastatic carcinoma Hodgkin s disease inflammatory disease of bone bone cysts and other bone conditions such as Paget s disease lipoid histiocytosis and inflammatory disease were aspirated In this series of 474 individuals a diagnosis was made in 268 cases In an additional 80 cases tissue was obtained which however was not specific and a diagnosis could not be made In 121 cases the aspiration yielded insufficient tissue for a diagnosis In five cases of malignant tumors the aspiration showed benign tissue and in one case of benign tumor the aspiration was reported as showing cancer tissue [48]

BONE MARROW

Bone marrow biopsy is a necessary diagnostic prerequisite in all hematologic disorders It is especially helpful in the study of anemia granulocytopenia, purpura and in the differentiation of multiple myeloma, lymphosarcoma, and the leukemias

The technic of bone marrow aspiration is as follows The patient is placed on his back The upper portion of the sternum between the second and the third rib is considered the site of choice After thorough skin cleansing the site of puncture is infiltrated with 1 per cent procaine including skin subcutaneous tissue and periosteum

The bone marrow biopsy needle is either of 16 or 18 gauge short beveled and 0 75 to 1 25 inches long It should be provided with a guard that can be set to limit the depth of puncture The skin over the site may be incised to facilitate the introduction of the needle With a rotary motion the anterior bony plate of the sternum is punctured A distinct give is felt when the needle enters the marrow cavity The stylet is removed and a 1 or 2 cc dry syringe is attached With slight suction a small amount of bone marrow is aspirated Large amounts may cause dilution of the specimen with blood The wound is then covered with dry gauze

The trephine method removes a button of bone with attached marrow and requires a skin incision and exposure of the sternum at the site of the biopsy Turkel and Bethell have introduced a special trephine needle in which

a plug of bone marrow is obtained with the simplicity of the aspiration needle

From the material obtained by either method several thin smears are made and the rest of the specimen is then placed in a preservative or prepared according to the directions of the pathologist or hematologist who is to study the material submitted

In 1947 Rubinstein [42] pointed out the advantage of aspirating bone marrow from the iliac crest because this region is less painful to the patient and safer because of the absence of important structures and organs that might sustain injury and because this procedure causes the patient less apprehension than when the sternum is punctured (cardiac area)

LYMPHATIC SYSTEM

Examination of the peripheral blood by means of the routine blood count with blood smears is always indicated in suspected disease of the hematopoietic and lymphatic systems

When a lymphomatous disease is suspected aspiration biopsy should not be done on a lymph node The entire node should be removed This will enable the pathologist to study the architecture of the node as well as its cytology It is advisable whenever possible to choose a node in a region other than the groin The inguinal region normally may contain varying sized lymphadenopathy of inflammatory origin

SPLENIC ASPIRATION

Aspiration biopsy of the spleen is considered to be an innocuous procedure when it is limited to aspiration of large spleens that can be readily approached by the abdominal route Bleeding and perforation of the gastrointestinal tract have been reported as complications of this procedure Morrison and his co workers noted no complications in 105 splenic aspirations [34]

The procedure is the usual aspiration biopsy technic using a 20 gauge needle The aspirate can either be studied as a smear preparation or put into preservative and prepared as other biopsy material is prepared for histologic study

Morrison and his co workers reported that the peripheral blood studies alone in the 105 cases in which splenic aspirations were performed yielded a positive diagnosis in 29 cases The bone marrow and peripheral blood combined yielded a positive diagnosis in 32 cases while the splenic aspiration the bone marrow and peripheral blood combined yielded a positive diagnosis in 102 patients

BRAIN

The diagnosis of a tumor of the brain is based on clinical findings x ray examinations including encephalograms electroencephalography and spinal fluid studies At exploration a biopsy may be taken or the tumor is removed and then submitted for histologic study

In 1930 Cushing and Eisenhardt introduced the supravital stain technics for the diagnosis of brain and spinal cord tumors In this technic the fresh tumor tissue is not allowed to dry but is stained while still wet The tissue is covered with a cover slip and the edges are sealed with Vaseline Thus the microscopic examination is made on wet tissue

More recently a dry smear technic has been used in several clinics [33] This technic is the same as that employed in the quick smear method for aspiration biopsy The fresh tumor tissue is smeared between two glass slides It is allowed to dry in air or it may be dried rapidly over a flame The smear is then stained with a solution of eosin for ten seconds and counterstained with methylene blue for fifteen seconds The smear is then given an acetone alcohol wash dried with chloroform cleared with toluol and mounted with balsam It is ready to be studied in a matter of several minutes

FIBROUS TISSUE AND FAT

Biopsy of tumors in these tissues may be done by the aspiration method or by exploration through an incision and removal of the entire tumor for histologic study

EDITORIAL NOTE

The technic utilized by us for biopsy of tumors of the soft somatic tissues combines the biopsy performance with the institution of definitive surgery at the same operative seance The procedure was developed in the hope that dissemination of tumor emboli

resulting from the trauma of the biopsy could be held at a minimum. The method is as follows: A tourniquet is placed proximal to the lesion, an *incisional biopsy is per*formed and a frozen section studied. If the report is a benign tumor, a local excision is effected and the tourniquet removed. If the report is sarcoma, a wide resection is completed and if an amputation is necessary, another tourniquet is applied proximal to the one already present and the amputation is effected between the tourniquets. This procedure has been adopted because of the observation that following the trauma incident to local excision of certain sarcomas the postoperative course is sometimes complicated by the presence of pulmonary symptoms. In these cases chest roentgenograms reveal patchy, mottled areas that are diagnosed either as bronchopneumonia or pulmonary infarcts. These patients usually return at later dates with definitive pulmonary metastases present at the very sites where the postoperative roentgen appearance of the lung lesion was due to tumor emboli showered there as a result of the surgical trauma to the primary neoplasm. The tourniquet biopsy and amputation are performed in an attempt to prevent the vascular spread of such embolic showers.

A technic has been developed by Joseph Greenberg* of scanning with isotopes (radioactive iodinated serum albumin) certain organs (the liver) to determine the site from *which a biopsy should be taken.* He has observed that neoplasms concentrate a significantly increased amount of radioiodine and by using this site of increased concentration as a guide for needle biopsy, he has obtained a 95 per cent positive histologic diagnosis.

* Greenberg, J.: Radioisotope Scanning as a Guide to Needle Biopsy of the Liver. *Am. J. M. Sci.* 233: 1, 1957.

CHAPTER 7

The Examination of Exfoliated Cells in Tumor Diagnosis

George N Papanicolaou
and
N Chandler Foot

GENERAL CONSIDERATION OF THE METHOD

Morbid exfoliative cytology is the term chosen to represent the diagnosis of pathologic conditions through the examination of cells exfoliated from surfaces or superficial lesions in contrast to that of sections of fixed and stained tissue which is *pathologic histology*

If cells are exfoliating from a tumor they will become mingled with the secretion from the surface bearing it and as such can be fixed stained studied and diagnosed If they are not exfoliating a negative report will result and it should be stressed that such a negative report is no indication that the patient is free from tumor A smear may be best considered as a preliminary to a biopsy if it is positive one may be doubly sure by confirming the diagnosis by taking a biopsy Suppose however that the preliminary smear shows malignant cells but no source of these (which could serve as the site for a biopsy) can be discovered on direct observation How should one proceed? In the presence of two or more conclusively positive reports (Class V) on smears and of strongly supporting clinical signs radical operation may occasionally be indicated without the additional proof of positive biopsies

With experimentation has come the devising of other methods aimed at the concentration of the cellular sediments for the preparation of cell blocks or at their entanglement in the meshes of Gelfoam sponge (Gladstone) In either case sections are prepared and the cells examined in these sections rather than in smears In this chapter it is our purpose to dilate only on the preparation and interpretation of smears references to the other methods are listed in the bibliography

An efficient cytologic diagnostic service cannot be easily undertaken by the average hospital pathologist as a part of his daily routine It requires at least fifteen minutes for the satisfactory examination of smears from one case thirty or forty such examinations would consume the entire time of a working day For this reason a laboratory of exfoliative cytology should be organized The equipment is comparatively simple and not expensive A few stains reagents and jars are all that is required

METHODS OF STAINING SMEARS

Since there is no stain that is specific for cancer cells various staining procedures may be used provided they fulfill certain requirements Of these the most essential are (1) a good definition of the nuclear chromatin as changes affecting the structure of the nucleus are most significant in cancer diagnosis (2) a differential staining of the various cell types encountered in smears and (3) transparency permitting the identification of overlapping cells or of cells embedded in mucus or blood

Hematoxylin-eosin stains the cytoplasm rather deeply and does not give good differential cytoplasmic staining Single polychrome stains have the disadvantage of a relatively poor definition of nuclear details Papanico-

laou s Hematoxylin OG6 EA36 method has been found satisfactory

*Staining of vaginal cervical and endometrial smears (Procedure No 268)**

1 After fixation in alcohol ether, smears are transferred *without drying* through 80 per cent 70 per cent and 50 per cent alcohols to distilled water

2 Stain in Harris hematoxylin(1) for 6 minutes

3 Rinse in distilled water

4 Dip in 0 25 per cent HCL (aqueous solution) 6 times

5 Place in running tap water for 6 minutes

6 Rinse in distilled water and run up through 50 per cent 70 per cent 80 per cent and 95 per cent alcohols leaving in each long enough to clear

7 Stain in OG6( ) for 1 5 minutes

8 Rinse in 95 per cent alcohol 2 changes

9 Stain in EA36(3) *or* EA50(4) for 1 5 minutes

10 Rinse in 95 per cent alcohol (3 changes) Dehydrate and clear by running through absolute alcohol a mixture of abso lute alcohol and xylol equal parts and xylol Mount directly from xylol with a cover slip using Permount gum dammar Canada bal sam or any other satisfactory mounting med ium still being careful not to allow smears to dry

Staining of sputum and various sediment smears (Procedure No 267)

(These smears must be handled carefully when transferring from one solution to an other as they wash off rather easily Smears will stick to slides better if fixed in alcohol ether overnight)

Steps 1 8 Same as steps 1 8 in Procedure No 268 for vaginal smears

Step 9 Stain in EA65(5) for 1 5 minutes

Step 10 Same as Step 10 in Procedure No 268

Staining solutions

1 Harris hematoxylin is prepared from the standard formula using ammonium aluminum sulphate but omitting the glacial acetic acid It is diluted with an equal volume of distilled water before using and filtered into a dark bottle for storage when not in use It should be reinforced by the addition of a small amount of fresh undiluted stock solution fairly often in order to maintain uniform staining results

2 OG6

Orange G	0 5 per cent so lution in 95 per cent al cohol	100 cc
Phosphotung stic acid		0 015 Gm

3 EA36

Light green SF yellowish	0 1 per cent so lution in 95 per cent al cohol	45 cc
Bismarck brown	0 5 per cent so lution in 95 per cent al cohol	10 cc
Eosin yellowish (water and alcohol sol uble)	0 5 per cent so lution in 95 per cent al cohol	45 cc
Phosphotung stic acid		0 200 Gm
Lithium car bonate sat urated aque ous solution		1 drop

All stains used in these preparations are Na tional Aniline and Chemical Company certi fied stains The formulae for OG6 and EA36 are taken from the article A New Procedure for Staining Vaginal Smears George N Pa panicolaou *Science* April 24 1942 95 438 also see Papanicolaou and Traut [2]

4 EA50 is a stain comparable to EA36 and may be obtained already prepared from the Ortho Pharmaceutical Corporation Rari tan N J *or its* distributors OG6 can also be obtained from them

5 EA65 is the same as EA36 except that the light green stock solution is half strength (0 25 per cent) It has the advantage of giving

* The technics that follow were taken from the instruction manual of Papanicolaou s laboratory

a lighter and more transparent staining which is desirable in smears containing much mucus The differentiation between the acidophilic and basophilic cells is better with the EA36 (or EA50) which is more important in va

Class IV Abnormal cells strongly suggestive but not fully conclusive for malignancy

Class V Abnormal cells conclusive for malignancy

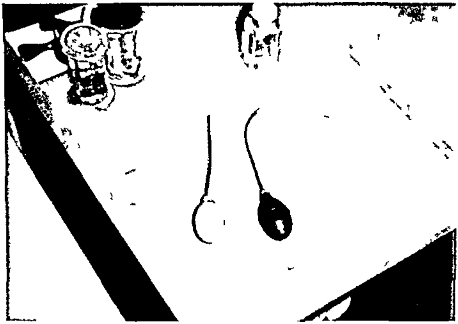


Fig 7 1 Paraphernalia for vaginal and uterine exploration Glass pipette laryngeal cannula spatula and swab in the foreground

ginal endocervical and endometrial smears Therefore EA36 or EA50 is preferable for vaginal endocervical and endometrial smears and EA65 for other types of smears although any of these stains may be used for all types of smears

CLASSIFICATION

In the evaluation of smears it is not always possible to reach a definite diagnosis There is an intermediate group in which findings are inconclusive A classification of reports in at least three groups is thus necessary the positive the inconclusive or suspicious and the negative In our laboratory a classification into five categories has been adopted This is as follows

Class I Absence of atypical or abnormal cells

Class II Atypical cells without features indicative of malignancy

Class III Cells with abnormal features suggestive but not fully conclusive for malignancy

Classes I and II are considered as essentially negative Class III as suspicious and Classes IV and V as positive

This classification offers two distinct advantages It permits a more exact evaluation of findings in both the positive and negative groups A Class V report from a qualified cytologic laboratory gives an assurance of practically 100 per cent accuracy Should one include all positive cases (Classes IV and V) in one group the accuracy according to our records is approximately 95 per cent

In the negative group the subdivision into Classes I and II permits a distinction between cases with entirely normal cytology (Class I) and those characterized by the presence of atypical though nonmalignant cells as in chronic inflammations benign papillary or polypoid growths etc (Class II) Class V is the only dependable group

The relative accuracy of diagnosis in the five groups of our series is approximately as follows

Classes I and II from 75 to 90 per cent

Class IV about 95 per cent
Class V over 99 per cent
Class III in this group the expectancy of true positive diagnosis is about 50 per cent

FEMALE GENITAL SYSTEM

Technics of Making Smears

VAGINAL SMEARS

Material from the vagina is usually copious and may be obtained from the posterior fornix with a slightly curved pipette (Figure 7 1), fitted with a rubber bulb The vagina must be in a resting condition no douche and no digital or instrumental examination should have immediately preceded the taking of a specimen The use of lubricating agents should be avoided The aspirated fluid is expressed onto a glass slide and immediately fixed in equal parts of alcohol and ether

Material from the exterior of the cervix may be obtained by swabbing with a cotton tipped applicator as well as by aspiration, some operators prefer to use wooden spatulae others curettes to scrape off bits of tissue as well as cells from the surface of visible lesions

ENDOCERVIX AND ENDOMETRIUM

In order to exclude from the specimen cells from the vagina and its fornices a laryngeal syringe (Figure 7 1) may be introduced into the endocervix and later reinserted into the endometrial cavity and fluid aspirated successively from these segments of the tract Catheterization of the tubal ostia is also possible but more difficult In this manner the location of a carcinoma suspected after the finding of malignant cells in vaginal smears may be fairly accurately determined in the endocervical canal or endometrial cavity

Interpretation of Smears

VAGINAL

The majority of cells found in vaginal smears may be grouped into two representative types (1) the superficial squamous (2) the parabasal The first type includes both noncornified (basophilic) and cornified (acidophilic) cells their relative numbers depending upon the stage of the cycle (Figure 7 2) In the cornified variety the nucleus is small and pyknotic The parabasal type (Figure 7 3) is encountered more frequently in menopause and amenorrhea and includes cells derived from the deeper layers of the vaginal and ectocervical mucosa Exfoliated cells of this type are round or oval and their nuclei are larger than those of the superficial cells

Vaginal tumors include nonmalignant epidermoid papillomas and carcinomas In the former, smears would give comparatively little information, there might be an increased exfoliation of superficial cells that might show atypical features but these would be difficult to interpret

PATHOLOGY OF CARCINOMA OF CERVIX AND VAGINA

The first histologic changes consist in irregularity of architecture and of anisocytosis and anisokaryosis of cells in all or any of the layers of the epidermoid membrane Certain cells become enlarged their nuclei enlarge and may become multiple They will show hyperchromasia and atypical mitotic figures Thickening of the nuclear membrane and of the chromosomes will be present to a variable degree As the process develops there is first 'atypia', the changes are atypical but not as yet definitely indicative of malignancy Such atypia may occur during pregnancy, when it appears to be a reversible phenomenon and to subside after delivery

As these alterations continue however the matter becomes different Anisocytosis brings about disorientation of cells the orderly progression from the columnar or spheroidal basal type of cell through the intermediate forms to the squamous superficial cell becomes uncertain and one begins to note shuffling of the elements Basal cells may be extruded as several layers of simple undifferentiated elements toward the surface, groups or single examples of them may come to lie intercalated among cells of an intermediate type Some of the elements may become much enlarged and may include multiple or single lobulated and enormous nuclei which are characteristic of neoplastic giant cells After all this has taken place but invasion of the underlying supportive tissue cannot be detected anywhere we speak of

Fig 7 2 Three examples of normal precornified and cornified squamous cells

carcinoma in situ One should be very guarded in making this diagnosis unless the pronounced atypia and metaplasia just de scribed are present

CYTOLOGY OF EARLY CARCINOMA (PREINVASIVE)

Smears from the vagina or cervix harboring carcinoma in situ will show more subtle and less strikingly abnormal changes in their ele ments than would those from a case of fully developed invasive carcinoma Probably the first element to excite suspicion is the dys karyotic cell in which the original cell type is retained but nuclear changes are prominent These changes consist of disproportionate nuclear enlargement distortion hyperchro masia and multinucleation These abnormal

Fig 7-3 Group of mixed superficial squamous and parabasal cells from a meno pausal smear

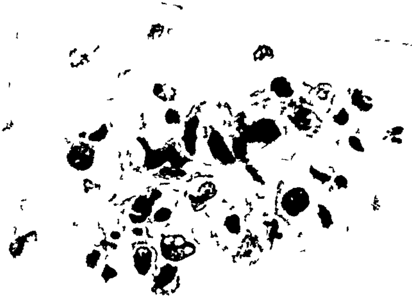


Fig 7-4 Cells characteristic of superficial cell dyskaryosis

cells may represent elements originating in the superficial intermediate navicular or the parabasal layers suggesting the terms *superficial* (Figure 7 4) *intermediate* or *parabasal* (Figure 7 5) *dyskaryosis* Whatever may be the change in the cell as a whole there is certain to be distinct nuclear atypia Some cytologists interpret these cells as definitely cancerous while others consider them to be precancerous In view of the fact that the presence of cancer cannot be definitely proved in some patients harboring such atypical elements and because reversibility has been noticed in the case of others it is probably best to apply the term *dyskaryosis* in reporting this finding

CYTOLOGY OF INVASIVE CARCINOMA

In this there is exfoliation of cells and cell clusters that are so frankly metaplastic that

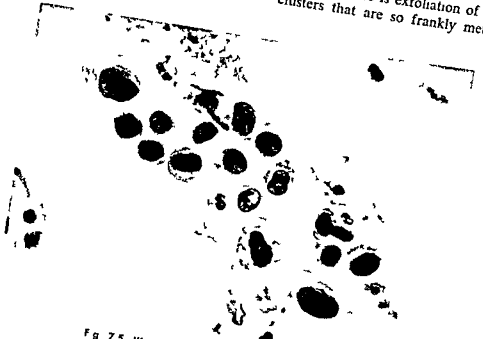


Fig 7 5 Illustrating parabasal cell dyskaryosis

Fig 7 6 Small cluster of malignant cells from advanced epidermoid carcinoma of cervix

they satisfy all the criteria of malignant change (Figures 7 6 and 7 7) They will show abnormal outlines (e g tadpole or serpentine) Smears from such carcinomas will also exhibit many distorted cellular elements The hyperchromasia and abnormal form and structure of their nuclei and the possible presence of enlarged nucleoli and karyosomes will differentiate them from any normal cells They are found to be grouped and crowded into clusters in which anisocytosis anisokaryosis disorientation and hyperchromasia are very prominent and the boundaries of the individual cells indistinct or lost With deeper invasion of the tissues and their vessels and degeneration of the neoplasm more exfoliation may be expected than would be the case in more compact normal tissue where scraping might be necessary in order to obtain a good specimen However those carcinomas which tend

Fig 7 7 Group of distorted malignant cells from advanced epidermoid carcinoma of cervix showing serpentine elongation and two atypical mitotic figures

Fig 7 8 Cluster of normal endocervical cells

to invade the underlying tissue rather than to fungate superficially will, of course, show *decreased* exfoliation and may thus be over looked The appearance of the smear, then, will depend largely upon the stage and direc tion of development of the tumor

ENDOCERVICAL SMEARS

The lining of the endocervix in its outer portions is composed of columnar epithelium with basally placed nuclei As the endome trium is approached in the inner extremity the mucosa goes over into a tissue closely resembling endometrial mucosa Thus two types of carcinoma may develop (*a*) epider moid carcinoma and (*b*) adenocarcinoma

In examining smears of the cervix the cytologist must first be acquainted with the appearance of the normal exfoliated cells (Figure 7 8) The cells are relatively small

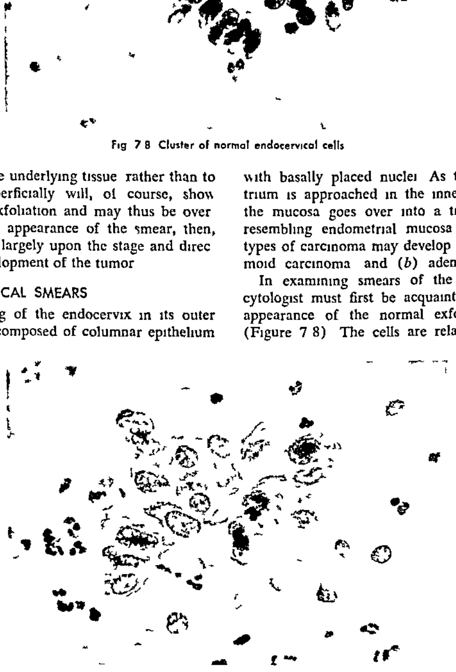


Fig 7 9 Cluster of endocervical cells showing cellular and nuclear hypertrophy attributable to subacute inflammation

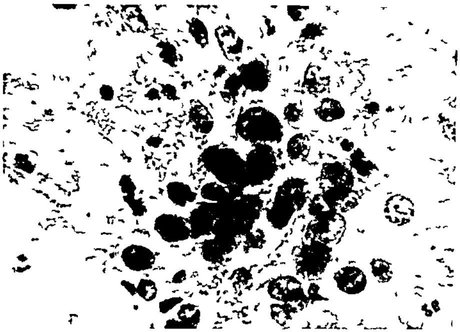


Fig 7 10 To illustrate endocervical cell dyskaryosis

and have a high nuclear cytoplasmic ratio

Branching complexes of rather large dense cervical epithelial covering cells may often be seen in smears from cases of chronic endocervicitis Cellular and nuclear hypertrophy irregularity in form and more intense staining may also be encountered (Figure 7 9) At first glance such cells appear to be malignant but an analysis of their nuclear characteristics will show that they are reasonably uniform and well differentiated In epidermidization clumps of the new epidermoid tissue may become detached and exfoliate The endocervical cells may show a dyskaryosis with nuclear changes corresponding to those found in cells desquamating from the lower reaches of the canal (Figure 7 10) in that case one must seek further evidence of carcinoma in situ In the endocervix this form of tumor rises near the junction of the two types of epithelium—

Fig 7 11 Vacuolated element from cervical adenocarcinoma

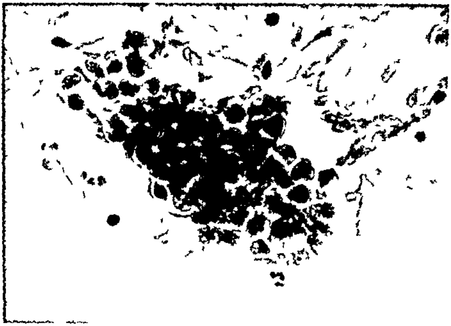


Fig 7 12 Cluster of normal endometrial cells recovered from a menstrual vaginal smear

the epidermoid and columnar but it may develop higher up through metaplasia of the columnar epithelium

In adenocarcinoma the exfoliated elements will be quite different from those in the epidermoid variety they tend to contain vacuoles of mucus and a basally situated nucleus suggesting glandular origin (Figure 7 11) They may be radially arranged in stellate clumps indicating papillary overgrowth They are anisocytotic and anisokaryotic and exhibit hyperchromasia of their nuclei In the rapidly growing *carcinoma simplex* there is an abundance of small completely nondescript cells with deeply stained nuclei As they resemble nothing in the normal cervix or vagina they are bound to arouse suspicion but they must be carefully distinguished from

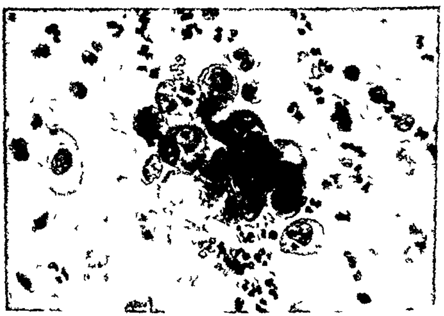


Fig 7 13 Cluster typical of adenocarcinoma of uterine fundus correctly diagnosed one year before final clinical confirmation

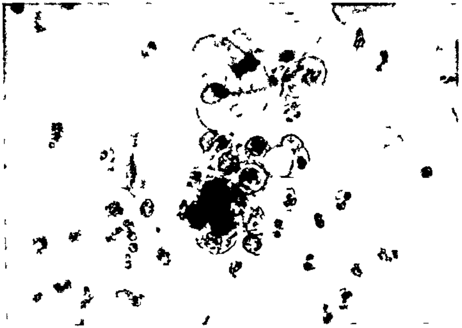


Fig 7 14 Cluster of cells from adenocarcinoma of fallopian tube recovered from cervical smear

the small more or less cuboidal elements from exfoliating endometrium which are not at all neoplastic

CERVICAL POLYP

This may exfoliate cells that are well differentiated and give little clue as to the existence of a tumor There is a considerable increase in exfoliating elements of either the glandular or the mucous type or squamous parabasal variety

ENDOMETRIAL SMEARS

Exfoliated endometrial cells may occur singly or in clusters and are normally found in vaginal or cervical smears during the menstrual bleeding They are smaller than the endocervical cells and because of their high

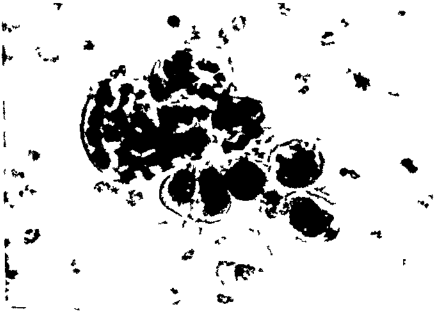


Fig 7 15 Adenoacanthoma showing squamous metaplasia Large cells at left contain many leukocytes

Fig 7 16 Cluster of cells from a cystadenocarcinoma of ovary found in an endometrial smear

nuclear cytoplasmic ratio the clusters appear very dense (Figure 7 12)

Adenocarcinomatous cells may be recognized by the general criteria of malignancy as well as by more specific criteria such as pronounced vacuolization and their frequent infiltration by leukocytes (Figures 7 13 and 7 14) Many necrotic cells are usually seen in the more advanced cases Adenoacanthomas may often be identified by the presence of clusters of vacuolated adenocarcinomatous cells showing pronounced epidermoid metaplasia (Figure 7 15) Occasionally in such clusters one may even see intercellular bridges Clusters of cells from a cystadenocarcinoma of the ovary may be found in endometrial smears and more rarely in endocervical or vaginal Such clusters are characterized by crowding vacuolization and their rosette form (Figure 7 16)

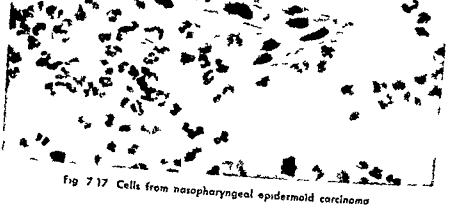


Fig 7 17 Cells from nasopharyngeal epidermoid carcinoma

SOURCES OF ERROR IN DIAGNOSIS OF VAGINAL SMEARS

The ubiquitous histiocyte is the cell that causes the most confusion in the mind of the beginner at exfoliative cytology It may become much enlarged take on a rather intense stain and assume some of the appearance of the malignant cell Histiocytes can usually be identified by (*a*) vague cellular outline (*b*) vacuolated cytoplasm possibly containing remnants of phagocytosed debris or entire leukocytes and (c) nucleus that is well differentiated often shows a reniform outline and does not vary in appearance from cell to cell It exhibits a very small and inconspicuous nucleolus Histiocytes may on occasions display much enlarged nuclei and relatively prominent nucleoli that may cause considerable insecurity A thorough search for transitional forms among the more typical histiocytes in a smear will facilitate their identification

RESPIRATORY TRACT

Method of Making Smears

The presence of malignant tumors in the respiratory tract may be determined in smears of sputum that may be obtained in the form of pure sputum or through bronchial lavage—in which case there will be some dilution with the fluid used for washing

Sputum should be produced by means of a deep cough one that originates low down near the diaphragm Mere clearing of the throat or a shallow superficial cough will raise little or nothing from the lower segments of the tract and is only practicable in the case of laryngeal or pharyngeal carcinomas (Figures 7 17 and 7 18) Bronchial lavage is carried out through a bronchoscope by introducing 2 or 3 cc of normal saline or Ringer s solution through a catheter and then reaspirating this Often it is feasible to pump the fluid back and forth thus setting up currents that may facilitate the collection of more cells from the mucosa

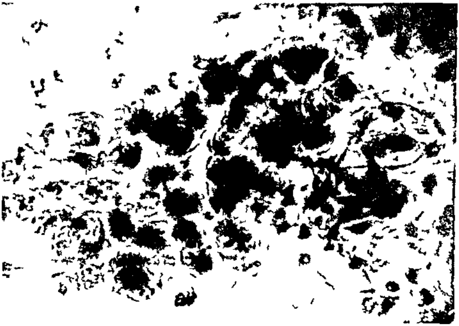


Fig 7 18 Large group of epidermoid cells from laryngeal carcinoma Note inter cellular bridges or prickles

Sputum is collected in 70 per cent alcohol by having the patient spit into a container partly filled with it when delivered to the laboratory it is already partially fixed and dehydrated Masses of this material are then smeared onto glass slides coated with egg albumin and glycerol and fixation is completed by submerging the smears in equal parts of ether and alcohol In the case of bronchial washings the aspirate is mixed with 10 cc of 70 per cent alcohol as soon as collected and the resulting mixture centrifugated before

Fig 7 19 Nonmalignant atypical cells from sputum

smearing the sediment In either case whether sputum or washings the smears must always be refixed in ether alcohol

Interpretation of Smears

NONMALIGNANT CELLS

The usual normal cells to be found in sputum are of the squamous variety from the oral cavity In bronchial washings they are chiefly ciliated or goblet cells from the bronchial mucosa Clusters of smaller undifferentiated cells from the deeper layers of the mucosa are often seen in smears of bronchial aspirations

There are two groups of elements that may cause confusion small epidermoid cells with pyknotic nuclei (Figure 7 19) often noted in connection with chronic laryngitis and possibly originating in the inflamed mucosa of the upper larynx and large dense cells that ap-

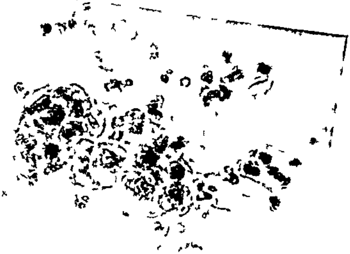


Fig 7 20 From the sputum of a patient with bronchiectasis

Fig 7 21 Histiocytes of lung (dust cells)

pear in the sputums of patients with bronchiectasis (Figure 7 20) The former can be dismissed with mention the latter are really confusing in the case of elderly patients in the cancer age These cells probably originate in alveoli abutting on bronchiectatic dilatations they are not found in the bronchioles or bronchi in sections but have been minutely described as being of alveolar origin They form clumps or clusters simulating neoplastic grouping Their nuclei are intensely stained but fairly well differentiated

Histiocytes may be found in varying numbers in connection with such conditions as chronic passive pulmonary congestion after inhalation of dust or particles of foreign material or lipoid pneumonia They are best recognized by the presence of contained

Fig 7 22 [illegible] epidermoid bronchogenic carcinoma Note small group of normal ciliated cells at [illegible] of field

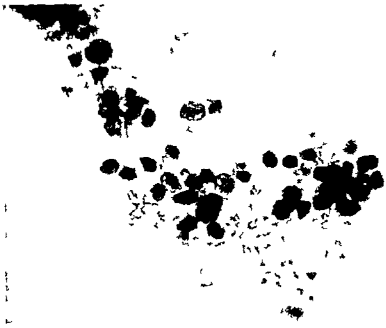


Fig 7 23 Oat-cell carcinoma of lung

phagocytosed foreign material (Figure 7 21) In lipoid pneumonia the fat brings about striking vacuolization of their cytoplasm

BRONCHOGENIC CARCINOMA

This group of carcinomas exfoliates readily into the bronchial lumina and may be diagnosed before it is visible on the x ray film or fluoroscopic screen Two instances of carcinoma in situ have been detected through the examination of smears In one there was a tiny ulceration of the bronchial mucosa grossly unrecognizable, in the other there was a small slightly ulcerated polyp from which cells were obtained by bronchial washing [3]

MALIGNANT TUMOR CELLS IN SPUTUM AND BRONCHIAL WASHINGS

Bronchogenic carcinoma is relatively easily recognized in sputum and bronchial washings

Fig 7 24 Pleomorphic type of bronchogenic carcinoma

the reason being that there is only a limited number of cellular possibilities in such material (*a*) blood cells (*b*) exfoliated tracheal or bronchial epithelium usually ciliated or of the goblet type (*c*) epidermal elements from the pharynx and oral cavity (*d*) pus and microorganisms Hence when large atypical cells are present they stand out in bold relief from the other familiar elements in the smear Not only are they recognizable through the usual criteria but their appearance is sufficiently characteristic for one to diagnose the type of carcinoma from which they arose

Epidermoid carcinoma (Figure 7 22) exfoliates many abnormal squamous cells that show a variable degree of keratinization whole epithelial pearls may be found as well The *oat cell carcinoma* (Figure 7 23) is recognized by the presence of small spheroidal elements not unlike lymphocytes but larger and with very dark staining nuclei which are apt to have a crenated or shriveled appearance Their oat shaped forms characteristically noted in sections are rarely seen in smears possibly because of the tendency of all cells to become more rounded after exfoliation *Pleomorphic carcinoma* (Figure 7 24) exfoliates very pleomorphic cells which are easily recognized as such and thus lead to a definite diagnosis *Alveolar carcinoma* (Figure 7 25) sheds rather copiously clusters or strips of cells that may vary considerably in size and sometimes contain vacuoles and exhibit multiple nuclei The grouping of the cells reminds one of an adenocarcinoma Vacuolization and eccentric nuclei are characteristics

Fig 7 25 Alveolar carcinoma of lung Note multinucleated cell at right

by which *adenocarcinoma* may be recognized (Figure 7 26)

URINARY SYSTEM

Method of Making Smears

Urinary sediments of voided urine from women may be heavily contaminated by vaginal elements therefore the specimen should be obtained by means of a catheter In men

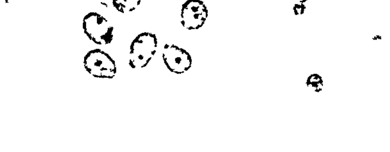


Fig 7 26 Vacuolated cells from bronchogenic adenocarcinoma

voided urine is suitable for examination although a catheterized specimen is more satisfactory Urine is immediately mixed with equal parts of 95 per cent alcohol before submitting it to the laboratory there it is centrifugated and the sediment is smeared on slides coated with adhesive material The smears are then fixed in ether alcohol without being permitted to dry as maintenance of moisture in smears until they are stained is of paramount importance

A specimen of urine from the bladder is analogous to one from the vagina inasmuch as it may contain miscellaneous cells from the bladder proper from the ureters or kidneys or in the male from the prostate or seminal vesicles Thus it is necessary after positive findings have resulted from the preliminary examination of smears of vesical urine to attempt to ascertain the origin of the suspected cells This is accomplished by the use of retrograde ureteral catheterization a specimen from the right ureter may show only normal cells while that from the left will reveal carcinomatous elements which must have come from a point somewhere between the debouchment of the left ureter at the trigone and the pelvis or calyces of the left kidney

Cells from prostatic carcinoma may be identified by special investigation The patient should be requested to void a little urine and stop the stream almost immediately this is labeled Specimen No 1 Then the prostate should be thoroughly but gently massaged which will occasion a flow of prostatic secretion through the penile meatus this is Specimen No 2 and it should be smeared on slides and fixed immediately in ether alcohol The patient is next asked to empty his bladder completely which will wash out the urethra and recover cells which might have been regurgitated into the bladder This is Specimen No 3 Finally a condom specimen of ejaculate may be obtained and some of this smeared and fixed as in the case of Specimen No 2 In this way there is a possibility of obtaining cells from the prostate which represents the sum of four procedures rather than one

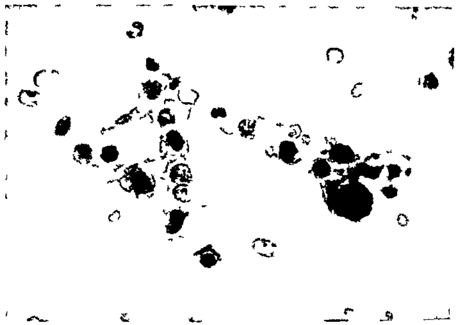


Fig 7 27 Atypical cells associated with renal calculus

Interpretation of Smears

NONNEOPLASTIC ELEMENTS IN THE URINARY SEDIMENTS

Unfortunately the lining of the urinary tract is one of the most frequent sites of metaplasia epidermoid metaplasia is common in connection with calculi glandular metaplasia is noted in long standing pyelitis ureteritis (very rarely) and cystitis (most usually) It

Fig 7 28 Multinucleated nonmalignant cells from ureteral catheterization

is most often met with in exstrophy of the bladder Hence in cases where there are stones the urine may present metaplastic cells in smears that will mislead the cytologist into diagnosing malignant tumor (Figure 7 27) This may be avoided by a careful study of the nuclei which will be found to be essentially normal and well differentiated

A puzzling feature is the occasional presence of giant cells sometimes so large that they contain fifty or more nuclei These are quite unlike the classic foreign body giant cell They are definitely epithelial their nuclei are precisely stained and spheroidal sometimes showing anisokaryosis and they possess definite nucleoli (Figure 7 28) Their cytoplasm though vacuolated contains little cellular debris Their source is yet to be determined They in no way indicate the presence of a neoplasm

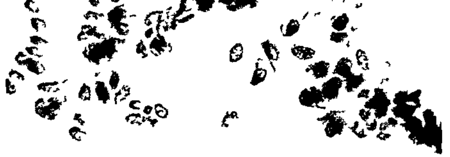


Fig 7 29 Cuboidal and columnar cells exfoliated from benign papilloma of bladder

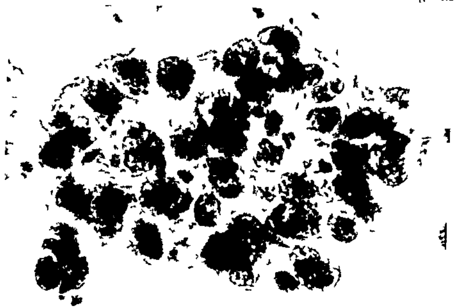


Fig 7 30 Fragment of early preinvasive carcinoma of renal pelvis detected by smears

TUMORS OF THE URINARY TRACT

Transitional Papilloma

This tumor may lie at any point between the trigone and the most rudimentary calyx of the kidney It is composed of innumerable frondlike papillae covered by elongated transitional epithelium Academically it is non malignant but so prone is it to recurrence and bleeding that urologists are wont to classify it as *papillary carcinoma Grade 1* Such a growth will exfoliate large numbers of approximately normal albeit attenuated transitional epithelial cells (Figure 7 29) In this case the cytologist must distinguish between desquamation from a tumor and increased desquamation from an inflamed lining membrane

Transitional Cell Carcinoma

This is the malignant analog of the papilloma just described it may be fairly well

Fig 7 31 Cluster of large cells from transitional cell carcinoma of bladder

Fig 7 32 Cluster from clear-celled carcinoma of kidney recovered from ureteral urine

differentiated or it may be pleomorphic and show many cytologic monstrosities (Figures 7 30 and 7 31) It very often undergoes epidermoid metaplasia which varies in degree from the mere production of squamous cells to that of prickle cells or cornified elements Occasionally the epithelium becomes totally dedifferentiated and produces cells so primitive and spherical that they remind one of lymphocytes Almost all these types may appear in the urine after exfoliation They are fairly readily recognized and diagnosed in smears

Renal Cell Carcinoma

This tumor sometimes breaks through into the renal pelvis undergoes necrosis and exfoliates characteristic cells but characteristic only to those who have seen them in urinary sediments as they are not the vesicular clear cells with which the pathologist is familiar in

Fig 7-33 Carcinoma of prostate (detected after prostatic massage) in voided urine

Fig 7 34 Cells from normal gastric mucosa (balloon specimen)

sections Renal cell carcinomas often show a series of cells ranging from small and granular to large and vesicular types (Figure 7 32) It is the former that appear in urinary sediments vesicular cells are a distinct rarity in this connection

PROSTATIC CARCINOMA

Prostatic carcinoma may be tubular, large celled or small celled multiacinar or alveolar, or epidermoid Carcinomas are not readily recognized as to type in prostatic smears unless they be of the epidermoid variety (Figure 7 33), but they may be distinguished from cancers of the urinary tract proper With observance of the four specimen method" we shall be able to recognize them earlier

DIGESTIVE TRACT

Methods of Making Smears

STOMACH

Methods have been devised to afford abrasion of a gentle type that will detach small

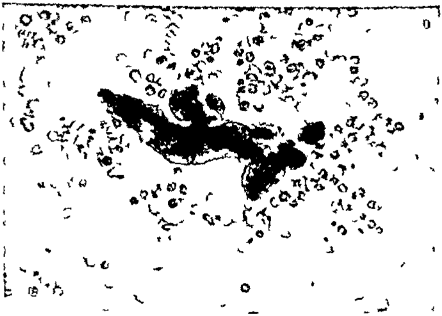


Fig 7-35 Elongated squamous cells from esophageal epidermoid carcinoma

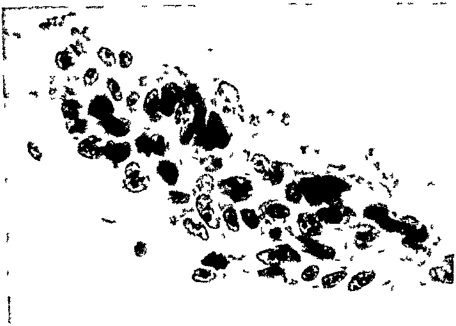


Fig 7 36 Atypical cells from gastric adenocarcinoma (balloon specimen) One mitosis at bottom of field

fragments of gastric tumor In this way much larger quantities of viable cells and shreds of tissue are obtained (Figure 7 34) there is less fluid and greater concentration of cells in the sediment and interpretation is correspondingly easier and more accurate

SMALL INTESTINES

By introducing the bucket on the Rehfuss tube into the duodenum it is possible to recover cells from carcinomas of the duodenum liver pancreas and biliary and pancreatic ducts

LARGE INTESTINE

Where biopsies are impossible on account of the high situation of an intestinal cancer saline enemas produce an unexpectedly large number of well preserved and readily identifiable cells from the colon and rectum The patient is given a thorough catharsis and put on a liquid diet for two days preceding the

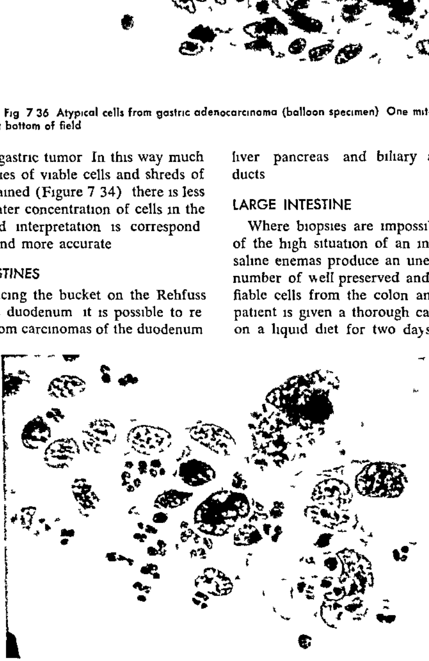


Fig 7-37 Extremely atypical cells from gastric adenocarcinoma (balloon specime)

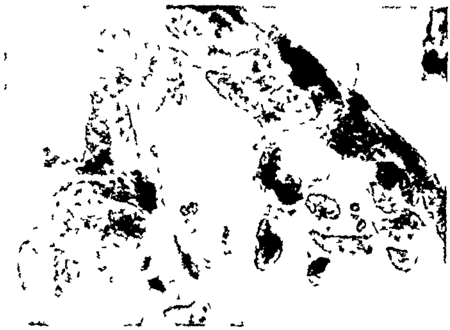


Fig 7 38 Carcinomatous cells in smear of colonic washings

administration of a high colonic enema of normal saline solution Of the return from the enema 100 cc are mixed with equal parts of 95 per cent alcohol and centrifugated the sediment being smeared onto slides coated with egg albumin glycerol adhesive and immediately refixed in alcohol ether

CELLS FROM THE ESOPHAGUS

The esophageal mucosa is composed of stratified epidermoid epithelium with mucous glands opening through it at intervals The cells that exfoliate are therefore chiefly epidermoid Smears of esophageal secretion afford a good means for the early diagnosis of carcinoma as they often contain many pearls and the highly keratinized elements As epidermoid carcinoma does not develop in the stomach any gastric smear showing these characteristics should at once indicate esophageal rather than gastric cancer

Fig 7 39 Cells from nonmalignant intraductile papilloma in mammary secretion

Fig 7-40 Fragment of early comedocarcinoma detected by means of smears of mammary secretion

Interpretation of Smears

CELLS FROM GASTRIC TUMORS

Two classes of carcinoma might be recognized adenocarcinoma that fungates into the lumen and scirrhous carcinoma Fungating carcinomas exfoliate large numbers of cells into the gastric secretions and these cells are atypical and relatively easy to identify the trouble is that so many of them are digested by the gastric juice and become practically amorphous Mucous carcinomas exfoliate signet ring cells that do not strictly fulfill the criteria of malignancy as they are well differentiated and regular in size and shape Scirrhous carcinoma usually produces only trivial areas of ulceration and hence exfoliates few if any cells With the use of the gastric balloon however much of this uncertainty has been eliminated (Figures 7 36 and 7 37)

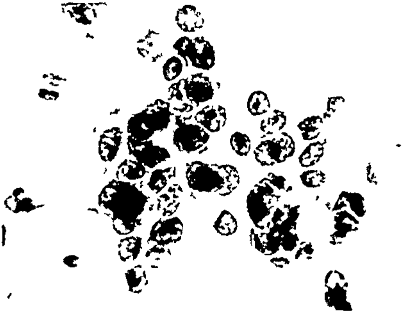


Fig 7-41 Mammary carcinoma first detected in smear of mammary secretion

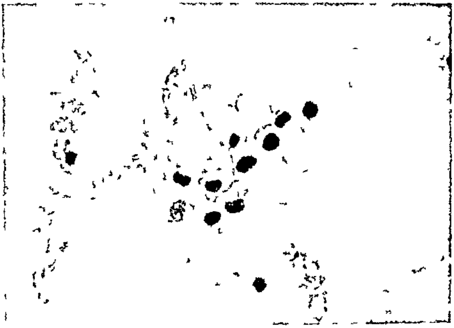


Fig 7 42 Histiocytes from pleural exudate Note reniform nuclei

Gastric carcinomas that exfoliate usually do not differ extremely from those of the covering layer of the gastric mucosa One must apply the criteria of malignancy very carefully before coming to a conclusion

CELLS FROM COLONIC TUMORS

Smears from centrifugated specimens of colonic and rectal washings may contain cells from polyps or malignant adenomas In the first case they will be present in large numbers and well differentiated In the second instance malignant looking cells may be found that have exfoliated from the surface of a tumor the pedicle of which is uninfiltrated by carcinoma Hence the growth is clinically nonmalignant On the whole however the results of examining smears from colonic washings of patients with intestinal carcinomas situated above the reach of the sigmoidoscope

Fig 7-43 Three mesothelial cells from peritoneal serous exudate

Fig 7-44 Cells from mammary carcinoma from exudate in pleural cavity

(where biopsy is impossible) have been accurate The cells of colonic carcinomas (Figure 7 38) exhibit sufficient aberration from the normal and enough metaplasia to make a positive diagnosis reliable If a malignant adenoma is diagnosed as carcinoma after being detected through positive smears the surgeon may recognize it as such at operation and content himself with its local removal

MAMMARY GLAND

Method of Making Smears

Obtaining a specimen should be very carefully performed Fluid may be expressed by gentle manipulation or, better, aspirated by a breast pump care should always be exercised not to indulge in massage of the organ, as this might detach cells into the lymphatics and cause metastasis

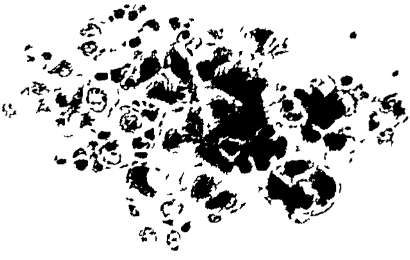


Fig 7-45 Cells of bronchogenic carcinoma in pleural exudate

Interpretation of Smears

NONNEOPLASTIC SMEARS

Fluid from breasts that are the site of chronic fibrocystic disease or intraductal papilloma will often show cells that may be misleadingly atypical (Figure 7 39) Cysts may be aspirated with a needle and the fluid examined in smears Histiocytes often appear in the form of well organized clusters as in chronic fibrocystic disease Here they must be clearly distinguished from malignant cells

CARCINOMA

As duct celled carcinoma (comedocarcinoma) grows in the canals of the breast it naturally follows that it would be the most likely type to appear in smears (Figure 7 40) Deeply seated scirrhous carcinoma would be less likely to be detectable

SEROUS FLUIDS AND EXUDATES

Samples of these in a reasonably fresh state should be mixed with at least equal parts of 50 per cent alcohol or they may be centrifugated if still warm and very fresh then after centrifugation the sediment may be smeared onto slides and fixed in ether alcohol Sediment may also be fixed in the centrifuge tube and the resulting button impregnated with paraffin and sectioned like ordinary tissue This is the ' cell block method

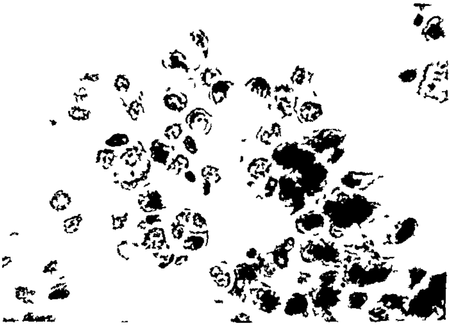


Fig 7-46 Ovarian carcinoma cells in smear of peritoneal fluid

Nonneoplastic Smears

There are many sources of confusion in these smears most of them dependent upon large numbers of histiocytes (Figure 7-42) and exfoliated mesothelial cells from the pleura or peritoneum (Figure 7 43) The former may be recognized by their good differentiation normally staining nuclei and faint vacuolated cytoplasm the latter are larger cells more compact, and are apt to present a serrated border zone that is distinctive

By the time that neoplastic elements have exfoliated into serous fluids diagnosis is only of confirmatory value the tumor has metastasized widely on the pleural or peritoneal surface (Figures 7-44 7 45 7 46 and 7-47) Nevertheless diagnosis is readily made Fluid from a hydrocele has produced typically carcinomatous elements in a case of embryonal carcinoma of the testis (Figure 7 48)

Other Fluids

While it is possible to make smears of fluid from the chambers of the eye the cerebrospinal fluid and other such liquids results have not been encouraging Neural tumors do not

exfoliate readily, cells from ocular tumors are difficult to recognize and to distinguish from pigmented normal elements The possibility is always there and it would be a pity to discourage the examination of any fluid produced by the human body

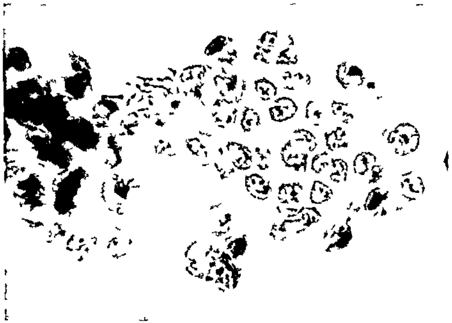


Fig 7-47 Arrhenoblastoma in peritoneal fluid

Fig 7 48 Testicular embryonal carcinoma exfoliating into hydrocele fluid

which it can be confused on clinical or histologic grounds

Neuroblastomas arising in the peripheral nerves appear to be more embryonal in nature than those discussed above, and are more prone to grow out in the form of epithelium with a minimum of neurites and these rather short protruding from multipolar cells The *neuroepithelioma* of peripheral nerves grows very rapidly, as a sheet or shelf entirely devoid of neurites Both of these highly malignant tumors of adults display their undifferentiated character in vitro Conversely, the ganglioneuroma which generally follows a benign course in children produces well differentiated sympathetic ganglion cells much like those that grow out from nonneoplastic sympathetic ganglia These neurons are also accompanied by large numbers of Schwann cells which are never seen in cultures from the malignant embryonal types of nerve tumors

Fig 8 1 Outgrowth from a leptomeningioma thirteen days in vitro stained with silver nitrate to show cement borders of flat cells resembling endothelium

Fig 8 2 Leptomeningioma twelve days in vitro fixed in Zenker's fluid and stained with phosphotungstic acid hematoxylin A variety of mesoblastic cell forms is shown here following the general lines of Maximow's polyblastic system

Fig 8 3 Outgrowth from a glioblastoma forty six days in vitro living phase contrast illumination Note large multinucleate bizarre generally stellate cells

In addition to the solitary benign nerve sheath tumors referred to above Murray and Stout have also cultivated malignant neurilemmomas which also produce characteristic Schwann cells in vitro [83] This observation has made it possible to retire the vague and often misleading term neurogenic sarcoma that has been applied indiscriminately to a variety of spindle cell sarcomas whether or not they could be shown to be related to the nerve sheath Since tissue culture will

Fig 8-4 Tufts of filamentous Schwann cells from a mediastinal neurilemmoma Twenty four days in vitro Zenker's fluid Delafield s hematoxyl n

Fig 8 5 Outgrowth from angle tumor (neurilemmoma of eighth cranial nerve) showing filamentous Schwann cells (A type) and macrophage l ke cells (B type) One of these is in mitosis Seven days in vitro Zenker s fluid phosphotungstic acid hematoxyl n

Fig 8 6 Malignant neurilemmoma from gluteal re g on Note hyperchromat c nuclei and variation in s ze E ghteen days in vitro Zenker s fluid phosphotungstic ac d hematoxylin

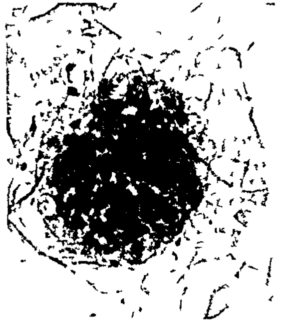


Fig 8 7 Metastat c sympathicoblastoma from th gh Seve teen days in v tro Bouin s f xative Bod an pro targol stain Note epithel al membranes from which neurites push out

distinguish between growths of Schwann ian origin and those of mesoblastic origin we are now able to separate the true fibro sarcomas from the schwannomas

Fig 8 8 Sympathetic ganglion cell from ganglio neuroma of lumbar peritoneal region showing branch ing dendritic processes Sixteen days in vitro Bouin s fixative Bod an s protargol stain

Lymphoma

The behavior of the Hodgkin s node in vitro distinguishes it sharply from neoplastic tissues in general and tends to align it with granulomatous lesions (In a recent review of the subject Bostick [6] concludes that the gradual accumulation of data increasingly favors the concept of a viral etiology for these lesions)

It is readily possible to differentiate Hodg kin s disease from lymphosarcoma of the lymphocytic type and from reticulum cell sarcoma The lymphocytic lymphoma behaves in vitro essentially like a normal lymph node evolving large numbers of lymphocytes and some macrophages and fibrous tissue The reticulum cell sarcoma produces few lympho cytes considerable fibrous tissue of an indif ferent nature replete with heavy reticulin fibers and usually sheets or clumps of flat polygonal (or sometimes stellate) cells that appear to be identifiable with the reticulum cells of the normal node

Fig 8 9 Early appearance of a Hodgkin s culture from cervical node Note reticulum cells lymphocytes lymphoblasts and intermediate cells Helly s fixative Delafeld s hematoxylin

Fig 8 10 Culture from Hodgkin s disease of m dias t num Note large cell with several nuclei and needle shaped pseudopodia also cell with vacuoles and in clusions Small black cells are lymphocytes Nine days in vitro; Bouin s fixative fuchsin ponceau and aniline blue

The cytologic picture of the Hodgkin s node in vitro varies considerably Fibrosed portions yield little except heavy fibrous tissue and a few lymphocytes But in any series of cultures selected from soft though not necrotic areas

there will appear within the first 48 hours varying numbers of lymphocytes macro phages and reticulum cells all more than usually active in migration and tending to have sticky surfaces Usually within this time will produce a similar pathologic reaction in cultures of normal tissues [42]

It is easy to distinguish lymphosarcomas in vitro from Hodgkin s disease since their whole appearance and behavior are grossly

Fig 8 11 Large multinucleate Hodgkin s cell with inclusions and needle shaped pseudopodia Small irregular objects creeping on this cell are lymphocytes Nine days in v tro living phase contrast illum na tion

there will be noticed near the explant some larger cells with two or three nuclei that are identified as Reed Sternberg cells Brilliant cresyl blue applied intravitally and Seller s stain in fixed cultures demonstrate cytoplasmic inclusions in the Reed Sternberg cells reticu lum cells lymphocytes and in a few fibro blasts If the culture is kept for a week or two longer the fibrin clot will be liquefied to some degree large multinucleate cells containing vacuoles and inclusion bodies will develop and some cell degeneration will take place in the outgrowth Cell free filtrates from Hodg kin s nodes and from tissue cultures of these different Their outgrowths do not stain meta chromatically with brilliant cresyl blue they do not evolve Reed Sternberg cells and they do not present the general granulomatous as pect of the Hodgkin s culture Lymphadenitis of inflammatory origin however may some times be confused with Hodgkin s disease in vitro Boeck s sarcoid and in children be nign lymphadenitis of unknown etiology may occasionally simulate the early stages of Hodgkin s cultures These do not however develop the massive inclusions vacuoles and enormous giant cells that appear in the later stages of Hodgkin s cultures this fact together

with the histology of the sections is sufficient to exclude Hodgkin s disease from the diag nosis A clearly positive Hodgkin s picture in tissue cultures within the first 48 to 72 hours is rarely if ever shaken later [83] nevertheless in the present state of our knowledge it is recommended that even such findings be checked with the morphology of the sections before a final diagnosis is given

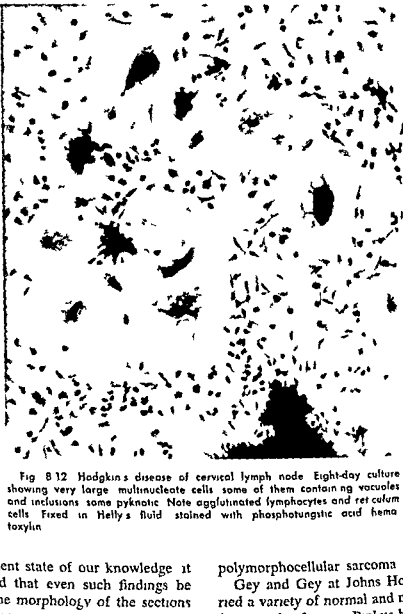


Fig 8 12 Hodgkin s disease of cervical lymph node Eight-day culture showing very large multinucleate cells some of them containing vacuoles and inclusions some pyknotic Note agglutinated lymphocytes and reticulum cells Fixed in Helly s fluid stained with phosphotungstic acid hematoxylin

Tumors of the Soft Somatic Tissues

It is the miscellany of the uncommon tumors of mesodermal derivation that yields perhaps the richest ore to the delver equipped with the methods of tissue culture Unable to identify exactly the cellular components of a rare tumor and give it a precise label the pathologist has often resorted to names in dicative of the shape of cells such as spindle round and giant cell sarcoma, or when he was able to detect more than one cell type has concocted compound terms mentioning them all and resulting in such monstrosities of terminology as fibromyxochondrosarcoma or polymorphocellular sarcoma

Gey and Gey at Johns Hopkins have car ried a variety of normal and neoplastic strains for periods of years Pinkus has isolated pure strains of malignant cells from several human tumors and has carried them in vitro for some nine months The glioblastoma multiforme and fibromyxosarcoma that he cultured appeared to be composed of a genetically inhomo geneous and labile cell material since the dominant cell types varied and changed with age in vitro A number of human malignant cell strains are now available for experimental studies but for classification and diagnosis

short term cultures are preferable

From a fortnight to a month has sufficed for most of our observations During this term growth patterns become clearly established and behavior often repetitive the requirements

Fig 8 13 Reticulum cell sarcoma of inguinal node Ret culum cells and lymphocytes Four days in vitro Helly s fluid Delafeld s hematoxylin

of space materials and labor become prohibitive if the period of cultivation is increased materially We have found it desirable to use a standard medium for the various types of mesoblastic tumors thus establishing a modicum of uniformity in treatment For tumors of nervous or of epithelial origin it is usually necessary to modify the proportions of this standard medium

HEMANGIOPERICYTOMA

The glomus tumor is an enlarged caricature of the highly specialized glomic arteriovenous anastomoses that are found at the cutaneous subcutaneous junction especially in the hands and feet and that have the function of shunting the blood rapidly from artery into vein without its passing through the capillaries These sometimes become hyperplastic and grow into tumors of insignificant size but of clinical importance because of the paroxysmal pain that they may induce Pathologists have long speculated on the nature and the function

Fig 8 14 Lymphocyt c lymphosarcoma from stomach Seven days in vitro Helly s fluid Delafeld s hematoxylin

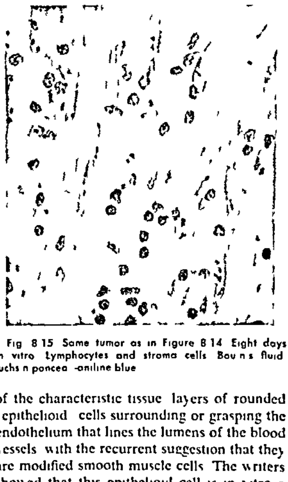


Fig 8 15 Same tumor as in Figure 8 14 Eight days in vitro Lymphocytes and stroma cells Bou n s fluid fuchs n poncea -aniline blue

of the characteristic tissue layers of rounded epithelioid cells surrounding or grasping the endothelium that lines the lumens of the blood vessels with the recurrent suggestion that they are modified smooth muscle cells The writers showed that this epithelioid cell is in vitro a branching structure very similar to the capil

lary pericytes described by Rouget and by Zimmermann [72] This led to the re examina tion of other obscure types of vascular tumors that did not have the organoid arrangement of the glomus tumor but had cells character structures in sections yet grew in vitro like a rather substantial mesothelial membrane Mesotheliomas can be either tubular or fibrous diffuse or localized benign or malignant and combinations of almost all these variants were

Fig 8 16 (*Upper*) Epithelioid cell from infiltrative glomus tumor of ankle (hemangio pericytoma) (*Lower*) Capillary pericyte from human heart (*After* Zimmermann 1923)

istically disposed outside the reticulin sheaths of the vessels It was then found possible to grade and classify these under the meaningful title of hemangiopericytoma and to separate them from other forms of angioma such as hemangioendothelioma (Figures 8 16 8 17 and 8 18)

MESOTHELIOMA

Similarly the fortuitous cultivation of a solitary fibrous mesothelioma from the pleura has led to the collection and grouping under one heading of a variety of types of solitary (or localized) tumors of the serous mem branes This pleural mesothelioma though it was entirely fibrous and showed no tubular assembled to illustrate this view As the result entities formerly decribed under eighteen or twenty different names are now brought to gether in one category of solitary (or local ized) mesothelioma (Figures 8 19 and 8 20)

Sano Weiss and Gault [95] have since cul tured a pleural mesothelioma that had clini cally a rapid diffuse spread yet whose sec tions showed the fibrosarcomatous appearance usually associated with localized and slow growing tumors Tissue cultures in the patient s plasma revealed its mesothelial character

PIGMENTED MELANOMA

Grand and Cameron studied pigmented melanomas from fish mouse and man Cells

that could be identified as epithelium were never observed in their many cultures of these growths though all cultures showed a rich outgrowth and multiplication of mesoblastic elements including fibrocytes macrophages and small and large melanoblasts These investigators were also able to show the similarity

Fig 8 17 Outgrowth from same tumor as in Figure 8 16 Twenty four days in vitro 10 per cent Formalin Bodian s protargol stain

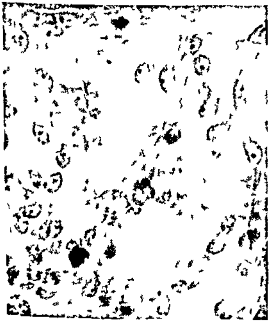


Fig 8 18 Pericytes encrusting endothelial outgrowths from same tumor as in Figure 8 16 Note capillary pattern Twenty eight days in vitro Kopsch fixative phosphotungstic acid hematoxylin

Fig 8 19 Outgrowth from a solitary fibrous mesothelioma of the pleura Seven days in vitro Zenker s fluid phosphotungstic acid hematoxylin

Fig 8 20 Higher magnification of outgrowth from same culture as in Figure 8 19

of the melanoblast in all three types of tumors and to identify it as the characteristic cell of melanoma In their cultures the melanoblast which was the source of melanin eliminated the pigment particles by clasmatosis This ejected material was often ingested by macrophages which thus became loaded with pigment but which never produced it *de novo*

Our observations on human malignant melanoma concur with the above in that the pigmented melanoblast is a spindle shaped or branching cell never growing in membrane formation (Figure 8 21)

Fig 8 21 Spindle-cell outgrowth from malignant melanoma of abdominal wall Heavily pigmented cells tend to round up because of mechanical factors involved in the accumulation of melanin particles Living twenty two days in vitro

Fig 8 22 Outgrowth from recurrent liposarcoma of right arm Note variation in nuclear size Seven days in vitro Zenker's fluid fuchsin ponceau

Fig 8 23 Sister culture from same tumor as in Figure 8 22 Zenker's fluid Weigert's iron hematoxylin

Fig 8 24 Large cell with multilobate nucleus from rhabdomyosarcoma of gastrocnemius Twenty three days in vitro Zenker's fluid phosphotungstic acid hematoxylin

LIPOSARCOMA AND RHABDOMYOSARCOMA

Because of the cellular pleomorphism that characterizes malignant neoplasms of both adipose and muscular origin and because undifferentiated liposarcomas are found that do not produce much fat and tumors of skeletal

Fig 8 25 *Multinucleate ribbons from same tumor as in Figure 8 24 Fifteen days in vitro Helly s fluid Weigert s iron hematoxyl n*

Fig 8 26 *Flat r bbons from same t mor as in Figure 8 24 N ne days n v tro Zenker s fluid phosphot ng s c ac d hematoxyl n*

muscle that reveal no cross striations in sections new *methods* of evaluating such growths are desirable

We have approached the problem by culturing liposarcomas and rhabdomyosarcomas each of which displayed in sections sufficient criteria of its type to establish the diagnosis The characteristics of these two tumors were even more divergent in vitro than in the sections It was found that the malignant lipoblasts could be distinguished readily from common fibroblasts on grounds of nuclear and

Fig 8 27 *Characteristic outgrowth from granular-cell myoblastoma (of female mammary gland) Note granular ribbon shaped cells and small corpuscular cells Thirteen days in vitro Zenker s fluid phosphotungstic acid hematoxyl n*

Fig 8 28 *G anula sp dle cells and i regular cells f om anothe myoblastoma of the female mammary gla d Twenty days in vitro Zenker s flu d phosphotungst c ac d h mato yl n*

cytoplasmic properties and of general growth pattern The typical viable reproducing spindle shaped tumor cell has a number of points in common with Chlopin s desmo blast of indifferent mesenchyme The very common variants from this form among the neoplastic cells appeared to be relatively non viable

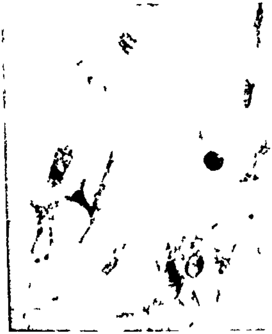


Fig 8 29 Living culture from xanthogranuloma of left gluteal region twelve days in vitro Stained supravitally with neutral red

Fig 8 30 Fibrosarcoma of male mammary region Eleven days in vitro Helly s fluid Weigert's iron hema toxylin

Fig 8 31 Fibrosarcoma of abdominal wall Seven teen days in vitro Zenker s fluid Weigert s iron hema toxylin

Fig 8-32 Outgrowth from synovial sarcoma of thigh Note spidery cells which are typical also of normal synovial outgrowths Twenty-eight days in vitro Zenker's fluid Harris hematoxylin

In the rhabdomyosarcoma myoblasts and ribbon shaped multinucleate cells appeared very similar to those that characterize embry onic or adult skeletal muscle outgrowths in vitro Large round multinucleate cells also were found such as are seen in sections and sometimes appear in cultures of normal

muscle Cross striations were not observed in our cultures they can however be expected to develop in tumor cultures (cf Timofeevskii [105]) as they do in cultures of normal skeletal muscle embryonic or adult (Figures 8 22 through 8 26)

Fig 8-33 Nineteen-day culture from same tumor as shown in Figure 8 32 silver stained for reticulin

OTHER TUMORS

Murray in cultivating three benign *granular-cell myoblastomas* of the uniform type has shown that this tumor has a distinctive form of outgrowth which resembles the cultured cells of normal and regenerating muscle as well as neoplasms of skeletal muscle more than it does the outgrowth from other tissue types that have been suggested for its origin [70] (Figures 8 27 and 8 28)

Xanthomas have been cultivated by Biedermann and Hofer who confirm their origin from the reticuloendothelial system [3] The single xanthogranuloma cultured by Murray and Stout lends itself to this interpretation [83] (Figure 8 29)

Three *synovial sarcomas* studied in vitro showed a growth rather similar to that of normal synovial tissue [78] The tumors produced a membranous or epithelioid growth whose cells appeared spidery but had regions of attenuated ectoplasm which was often continuous with that of its neighbors This type of outgrowth was combined in various proportions with a tissue composed of rather flattened spindle cells that were distinct from the fibroblast Both these modulations of the neoplastic synovial cell produced reticulin in vitro though the normal synovial cells cultured did not It was suggested that the synovial sarcoma is a distinct type of neoplasm exhibiting certain similarities to the mesothelioma [45] (Figures 8 32 and 8 33)

A variety of other tumor types including tumors of the skeletal system [59 62] have been described For reasons of space account of these is omitted

Clinical Application

In the present state of our knowledge the combination of tissue culture with routine methods is advised for differential diagnoses involving liposarcoma rhabdomyosarcoma mesothelioma or other ambiguous growths of the soft parts

PLEURAL AND PERITONEAL EFFUSIONS

Hengstmann (1941) using tissue culture methods observed that the diagnosis of carcinoma could often be established in effusions This observation has been confirmed by others

EPITHELIAL TUMORS

For the purpose of either classification or diagnosis tumors of epithelial origin have been the least rewarding Epithelial cells in general appear to be the most delicately adjusted to the exact physical and chemical constituents of their normal environment they react in an exaggerated manner to small variations in these Consequently in a tissue culture where usually a far greater range of differences exists than is consistent with life in the homothermal individual epithelial cells show corresponding modulations usually toward the general and most primitive or versatile cell form When explanted these cells do not differentiate in vitro but rather tend to establish less specialized forms and functions than the parent tissue maintained in vivo All forms of epithelium tend to adopt the squamous habit in vitro [37] however this is not an absolute rule [10] Pigmented epithelium may continue to produce pigment [29] squamous-cell epi

thelioma may produce intercellular bridges and pearls [50] thymoma may produce abortive Hassall s bodies [80] mammary carcinoma, mixed parotid tumors and pancreatic ade nomas may form acini and cysts [12] and

Fig 8 34 Twelve day culture from a persistent thymus gland with nodular epithelial hyperplasia in a woman of twenty seven with myasthenia gravis Note early form of Hassall s corpuscle Bouin s fluid fuchsin ponceau ani line blue

glandular epithelium such as thyroid adenoma may produce its characteristic secretions [83] (Figures 8 34 and 8 35) Generally speaking however these manifestations are rare and they tend to be confined to the benign or less malignant tumors

Weitzmann notes that malignant epithelial cells can often be distinguished from normal by the large size and bizarre shape of the nucleolus Glatthaar employs phase contrast microscopy in combination with tissue culture in prognostic studies of precancerous lesions of the cervix Hirschberg et al have shown that the human glioblastoma which is sus ceptible in vitro to 8 azaguanine is almost totally lacking in an enzyme that can deam inate this substance to the harmless compound 8 azaxanthine On the other hand by homog enate tests normal human glial tissue was found to be extraordinarily high in content of this deaminase

SUMMARY

In summary it may be said that as a means of elucidating the cellular origins and relation ships of neoplasms tissue culture has data of unique importance to offer As a diagnostic method it is largely accessory to the con ventional procedures in its present state of development but depending on the material at issue it may function at one of the following levels of value

1 It may afford the best method both quicker and surer than routine pathologic sections and independent of them The ex ample of this is the sympathicoblastoma

2 It may afford a very good method in tensifying the distinctive characteristics of the tissue in question but best used in combina tion with clinical and routine pathologic observations The neurilemmoma lymphoma and serosal effusions afford examples

3 It may provide a useful method for dis tinguishing among several alternatives left open by clinical and histologic methods for example the choice between liposarcoma rhabdomyosarcoma and fibrosarcoma or myx oma A mesothelioma may be detected by this means or a diagnosis of neuroepithelioma confirmed

Fig 8-35 Living culture (five weeks in vitro) from benign unencapsulated islet-cell ad noma of pancreas Stained supravitally with *neutral red* which also stains normal islands in vivo

4 It may be of no particular benefit in diagnosis though useful in collecting general information This level applies by and large to the commoner epithelial types of tumors in which the diagnosis is largely based on topographic arrangement of cells (which is lost in vitro) and on number and type of mitoses (of which the sections are a truer gauge than cultures)

Surgery

CHAPTER 9

General Principles of Preoperative and Postoperative Care

Irving M Ariel
and
George T Pack

The application of physiologic principles has permitted the patient suffering from cancer to be conducted safely through radical surgical procedures Fluid crystalloid and colloid balances must be rigidly maintained in the patient with cancer because of the deleterious effects of certain cancers upon the patient s metabolism and hence upon his ability to withstand and to recover from the surgical attempt to ablate the neoplasm

This discussion will present the normal balances and the routes by which certain imbalances develop Throughout average values shall be presented and normal values shall be equated to an average normal person weighing 70 kg

MEASUREMENT OF FLUID AND SOLUTE BALANCE

For the average surgical patient who undergoes a relatively minor procedure elaborate measurements are not indicated for a determination of the plasma content of different constituents will present an index of the patient s balance Table 9 1 presents the normal values of the various plasma constituents ordinarily determined in the surgical patient

NORMAL PHYSIOLOGY OF FLUIDS, CRYSTALLOIDS, AND COLLOIDS

Water Balance

As the body is essentially a suspension of a relatively small quantity of solid (40 per cent) in water the importance of understanding fluid dynamics in the surgical patient becomes obvious Figure 9 1 shows graphically the distribution of water within the organism About 60 per cent of the body is water which equals the large volume of 42 liters

The maintenance of an exact physical environment within the body cells is effected by the compartmental distribution of available water between the cells per se and the interstitial spaces This separation of body water into two distinct compartments (intracellular and extracellular) represents an evolutionary development whereby the extracellular compartment absorbs the brunt of the massive influx of water and metabolites and maintains a constancy of the cellular structure that deviates little during normal states

Abnormalities of balance between the individual and his external environment (abnormal losses of water and solutes from the individual or excessive administration of one or both of these substances to the individual) must be distinguished from those abnormalities of balance between the cellular mass and its environment—the interstitial space Thus a low plasma chloride (an index of the extracellular content of the ion) could be due either to excessive losses from the organism (vomiting) or an abnormal ingress of the chloride ion into the cell The distinction of course is important for therapeutic consideration

One may thus visualize the cells of different tissues of the organs containing large quanti

TABLE 9 1 —NORMAL VALUES OF CERTAIN BLOOD CONSTITUENTS

Hematocrit	40 to 45 per cent packed red cells
Red blood cells	4 to 5 million cells per ml
Plasma protein	6 5 to 7 5 Gm per cent
Blood nonprotein nitrogen	15 to 30 mg per cent
Blood urea nitrogen	5 to 15 mg per cent

Body waters are presented in Figure 9 1
Normal plasma electrolyte concentrations are shown in Figure 9 2
They are expressed in milliequivalents per liter

Na	1 mEq =23 mg	obtained by	mg per cent × 10 − atomic wt × valence (1) = mEq/l
K	1 mEq =39 mg		
Cl	1 mEq =36 mg		
HCO	1 mEq =67 mg		

A conversion chart (see facing page) is helpful to convert one value to the other for those laboratories that report the values in mg per cent

ties of water and suspended in a water environment The quantity of water in different tissues varies as follows

Body tissue	*Per cent water*
Cerebrospinal fluid	99
Blood plasma	92
Muscle	75
Liver	70
Fat	10
Bone	20
Tooth enamel	3

The water balance of a normal individual with the external environment presents base line indexes that can be related to the patient undergoing surgical procedures These are summarized in Table 9 2

Crystalloid Balance

The division of water into the three theoretic compartments depends essentially upon an osmotic gradient of the various crystalloids Figure 9 2 presents an illustration of the concentration of the various salts in the different body compartments The difference in concentration of the crystalloids between the plasma and the interstitial space is due essentially to the oncotic pressure exerted by the plasma proteins as expressed by the Gibbs-Donnan equilibrium factor A marked difference of electrolytes is evident between the extracellular compartment and the intracellular compartment It may be assumed that the intracellular mass comprises that portion of the organism in which vital processes occur The maintenance of an exact fluid and crystalloid state must be necessary to maintain vital function The extracellular compartment (interstitial space and plasma) are concerned essentially with the logistics of delivering necessary ingredients to the cells and disposing of waste products The salt content of the extracellular space provides a medium for the maintenance not only of the fluidity of the cell but also the crystalloid content of the cell The total content of the different crystalloids within the different compartments is

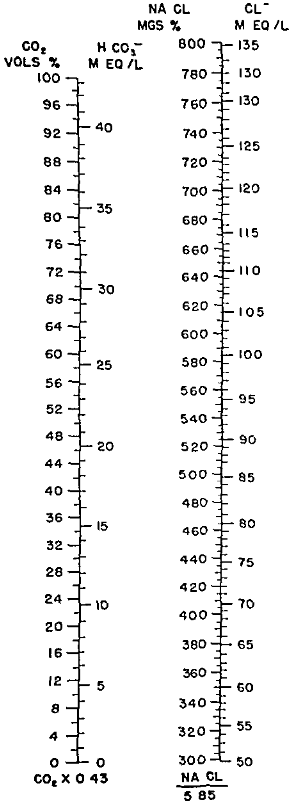
TABLE 9 2 —DAILY NORMAL INTAKE AND EXCRETION OF WATER

Water intake	*ml*	*Water loss*	*ml*
Water ingested	1500	Insensible perspiration	1000
Water contained in food	1100	Urine	1600
Water of oxidation	300	Feces	300
Total average	2900		2900

These values naturally have wide variations The man drinking 5 liters of beer will urinate an almost similar amount. Frank perspiration may expel over 6 liters of water

TABLE 9 1 (*Continued*)

(Conversion Chart)



DISTRIBUTION OF BODY WATER

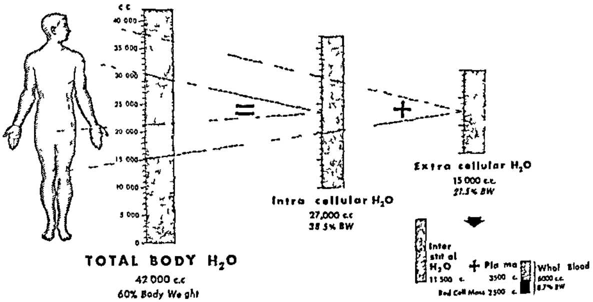


Fig 9 1

THE CONCENTRATIONS OF ELECTROLYTES IN PLASMA INTERSTITIAL FLUID AND INTRACELLULAR FLUID

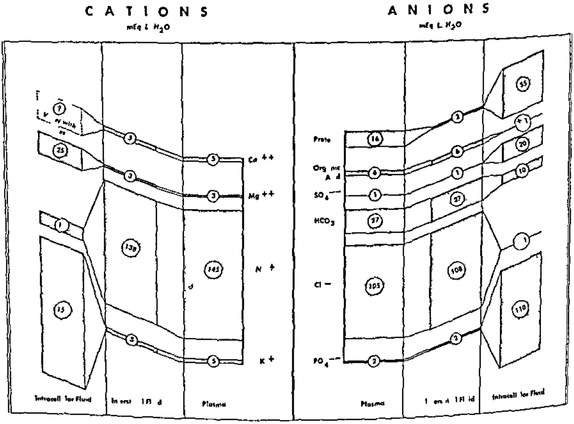


Fig 9 2

demonstrated in Figure 9 3 It will be noted that sodium and chloride are essentially extracellular and that measurements of the plasma concentration of these ions usually represent their true corporeal quantity Con retained within the organism If there is a loss of all electrolytes water cannot be retained even though administered copiously and a dehydration of depletion will develop even in the presence of needs The fluidity

THE TOTAL QUANTITIES OF ELECTROLYTES IN THE DIFFERENT FLUID PHASES
(PLASMA, INTERSTITIAL FLUID AND INTRACELLULAR FLUID)

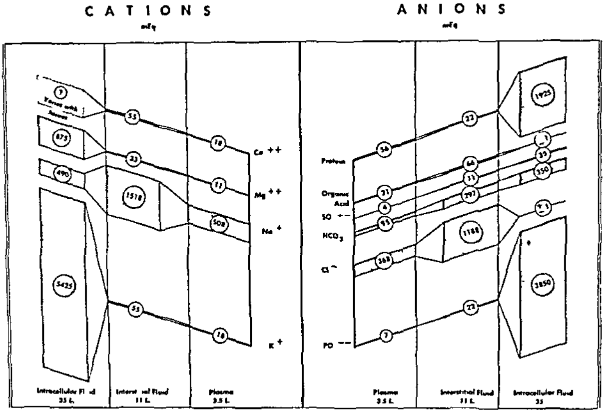


Fig 9 3

trariwise potassium which is essentially intracellular and is present in the plasma in small quantities does not lend itself to an exact corporeal determination by measurements of its plasma concentration Thus a large egress of potassium from the cells into the plasma (as occurs in oliguria) will present a high plasma value in the presence of a cellular defect of this ion

Electrolytes have essentially four main functions which are discussed in the following paragraphs

(1) They control the content and distribution of water within the body and (2) maintain osmotic pressure If the organism contains its normal electrolyte content as shown in Figure 9 3 a given quantity of water will be of the plasma is maintained by its protein content whose oncotic pressure retains fluid in the vascular system In the presence of plasma protein deficiency adequate water will not be retained in the plasma and will diffuse into the interstitial spaces producing overt edema (starvation or war edema) The selective distribution of electrolytes within the organism dictates the water content of the different body compartments Thus the quantity of potassium (essentially an intracellular ion) will influence the water content of the cells and the content of sodium and chloride (essentially extracellular ions) will determine the water content of the extracellular compartment (interstitial spaces and plasma) with the selective distribution of water within this

compartment determined by the plasma protein content It accordingly becomes ap parent that if a deficiency of sodium chloride exists, the water in the extracellular space becomes hypotonic and, according to Donnan equilibrium water will then enter the cells and swell producing an intracellular edema If an excess of sodium chloride exists either from large ingestion of it (salt fish pretzels etc) or from loss of pure water, the extracel lular compartment becomes hypertonic and water comes out of the cells into this com partment in answer to osmotic demands pro ducing an intracellular dehydration (Figure 9 4) The well integrated control mechanisms of the organism originating in the osmo receptor center of the brain reacts to these changes in osmotic pressure When the ex tracellular fluids become hypertonic anti diuretic hormone is secreted and all water is carefully retained Conversely when the extracellular fluid compartment is hypotonic antidiuretic hormone is not secreted and water is liberally excreted from the body

TYPES OF WATER AND SALT DEFICIENCY

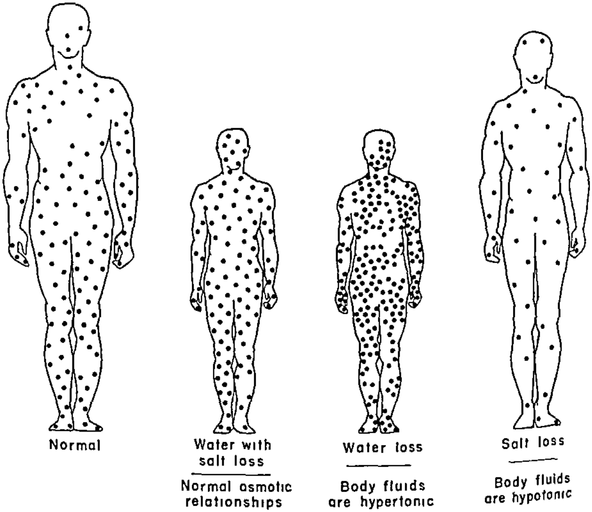


Fig 9-4

(3) Electrolytes determine neuromuscular irritability Sodium and potassium increase neuromuscular irritability while calcium and hydrogen decrease it Thus a decrease of calcium magnesium or hydrogen (alkalosis) increases the reactivity of the musculature The tetany of alkalosis is an example of this phenomenon Increase of potassium in the plasma affects the irritability of heart muscle which may produce serious sequelae

(4) Electrolytes participate in maintenance of acid base balance The maintenance of an

exact pH is of prime importance and is guarded zealously by the organism The balance is maintained by the ratio of the concentration of bicarbonate to carbonic acid (Henderson Hasselbalch s equation) The normal ratio of 27 mEq per liter of bicarbonate to 1 35 mEq per liter of carbonic acid maintains the normal pH at 7 4 The content of these elements is determined by the respiratory center and with an increase of carbonic acid (acidosis) hyperpnea becomes evident as the only clinical sign of acidosis and the means whereby the body attempts to blow off excess carbonic acid The kidneys play a major role in maintenance of electrolyte neutrality by excreting or withholding the quantity of base available to combine with the bicarbonate The method of maintaining an exact acid base (anion cation) balance is complex and beyond the scope of this discussion

TABLE 9 3 —THE AVERAGE NORMAL INTAKE AND LOSS OF ELECTROLYTES PER 24 HOURS (Sodium potassium and chloride)

	Sodium mEq /24 hr	*Potassium* mEq /24 hr	*Chloride* mEq /24 hr
Intake	125	75	100
Output	110	60	120

Expressed in another way the body may be viewed as a cellular mass that has two types of circulation The one is concerned with the exchanges with the exterior (blood circulation) whereby wastes are disposed of (CO_2 exhaled urea etc excreted) and the necessary raw materials introduced (oxygen and nutrients) The second circulation (interstitial circulation) is concerned with the deliverance of nutrient digested materials to the cells and the carrying of wastes (lactic acid etc) from the cells to the plasma for disposal Controlled electrolyte and water balances are necessary for the maintenance of these two separate but integrated circulations The daily balance of sodium potassium and chloride is presented in Table 9 3

Colloid Balance

Protein one of the most essential protoplasmic ingredients has defied for the most part an understanding of major portions of its metabolism as pertains to the surgical patient Little is known about the mechanism of egress of plasma proteins into the tissue parenchyma or the metabolic demands that determine the dynamic ebb and flow of the plasma proteins as described by Whipple The maintenance of a normal plasma protein concentration in the surgical patient is essential because protein oncotic pressure contributes significantly to the maintenance of the plasma water Proteins further maintain osmotic neutrality by virtue of their base binding capacities they combat infection by forming antibodies are actively engaged in all reparative body functions are an essential nutrient and are engaged in the fabrication of hormones Albumin contributes the greatest oncotic pressure and the globulin content produces antibodies etc All body proteins are engaged in one function or another and for practical purposes it must be assumed that all are essential and that there are no reserve proteins which can be utilized during periods of protein deprivation

Hypoproteinemia can be due to several causes

1 Deficient intake (starvation)

2 Liver disease—albumin appears to be fabricated essentially in the liver

3 Abnormal losses—ascites infections etc

The administration of saline solutions aggravates edemas the result of hypoproteinemia

The quantity of proteins necessary for a normal male has been estimated at 70 Gm per 24 hours Approximately 5 to 10 Gm of nitrogen are excreted in the urine per day representing the end product of protein catabolism 6 25 Gm of protein being represented by 1 Gm of nitrogen

The ingested proteins enter the metabolic pool after having been digested and function in answer to metabolic demands having cer

tain unexplained priorities Priority is given to the manufacture of red blood cells over fabricating plasma proteins Thus in an anemic hypoproteinemic patient it becomes essential to replace red cells by transfusion so that any administered protein will follow the metabolic route for manufacturing plasma proteins

TABLE 9 4 —NUTRITIONAL COMPOSITION OF THE HUMAN ADULT MALE (*After* Elman)

Total weight	*70 6 kg*
1 Water	40 kg
2 Protein	10 kg
3 Fat	9 kg
4 Ash	3 kg
5 Carbohydrate	0 6 kg
6 Plus vitamin	

(From Elman [2"] *courtesy* Appleton Century Crofts Inc)

Other Nutritional Needs

CALORIES

The normal resting adult requires almost 1600 calories per 24 hours best supplied by carbohydrate (4 calories per Gm) and fat (7 calories per Gm) Proper protein metabolism cannot occur in the absence of adequate quantities of carbohydrates

VITAMINS

Vitamins permit proper metabolism of food and their intake should accompany food and never be a substitute for the essential food stuffs

The normal intake includes

Vitamin C	75 mg
Thiamin	1 5 mg
Riboflavin	2 mg
Niacin	15 mg

and pantothenic acid and pyridoxine

Increased amounts are needed for the depleted patients and for specialized demands Thus increased amounts of vitamin C are necessary for proper wound repair etc

The nutritional composition of the human adult male has been summarized by Elman in Table 9 4

ABNORMALITIES OF FLUID BALANCE

Abnormalities of the normal fluidity of the surgical patient may occur from one of three avenues or a combination of these They are

1 *Abnormal losses (or gains)* to the external environment These include excessive perspiration vomiting diarrhea any abnormal drainage hemorrhage etc Included in this category would also be failure of adequate intake

2 *Physical disruption of fluid distribution* Included in this group would be abnormal fluid accumulations in a burned or otherwise traumatized region in inflamed sites or as a result of circulatory disturbances It must be recalled that when such abnormal accumulations occur in one region they do so by depleting another portion of the organism

3 *Metabolic disturbances* Changes in osmolar concentrations affect the distribution of water between the cells and extracellular space as discussed above The cell membrane permits the free transport of water into and out of the cell in answer to osmotic demands Other substances such as glucose and urea also enter the cell to effect a normal distribution throughout the entire body of these substances and thereby also affect the cell s hydration The cell membrane is semipermeable to electrolytes permitting the free ingress of potassium a selective ingress of sodium in response to the maintenance of acid base balance and an almost complete isolation attitude as pertains to the chloride ion Other larger molecules such as certain proteins inulin etc do not penetrate the cell membrane Thus the osmotic state of the organism (total number of electrolytes) will determine

the distribution of water between the cells and the extracellular compartment In addition recent experiments have demonstrated that a breakdown of the cell membrane s selective permeability may occur under certain conditions (anoxia malaria) with a swamping of the cell with all the materials from the extracellular compartment

Table 9 5 presents a classification of edema and dehydration that may occur in a surgical patient and Figure 9 5 demonstrates graphically some of these abnormalities It thus becomes essential to think in terms of total distribution as well as quantity and to try to correct both defects with the choice of suitable repair substances Changes within the

TABLE 9 5 —Classification of Edema and Dehydration

Bound water (Osmotically inactive)	*Osmotically active*			
	Extracellular compartment	*Intracellular compartment*	*Cause*	*Remarks*
1 After injection of certain hormones (estrogens) 2 3 5 Gm of water deposited with each Gm of protein 3 1 5 Gm water deposited with each Gm of glycogen (Fat is deposited dry)	1 Edema	Normal	Administration saline solutions aggravated by hypoproteinemia	After operation more administered saline remains in interstitial compartment The extracellular space of the lungs is four times greater than other tissues hence in this type of edema great quantities of water are present in the lungs
	2 Edema	Dehydration	After administration of hypertonic solutions	
	3 Edema	Edema	Local regions following trauma Administration of sodium chloride to patients with hypokalemic alkalosis	
	4 Dehydration	Normal	When pure water is drunk by an individual losing gastric juice Hemorrhage Rapid water deficiency	Water thus becomes a dehydrating agent Experimentally produced by intraperitoneal injection of water and later removal of the solution
	5 Dehydration	Dehydration	Severe dehydration from any cause	
	6 Dehydration	Edema	Metabolic alkalosis	May be converted to bicompartmental edema by rapid administration of NaCL
	7 Normal	Edema	After partial correction of metabolic alkalosis	
	8 Normal	Dehydrati	ation	

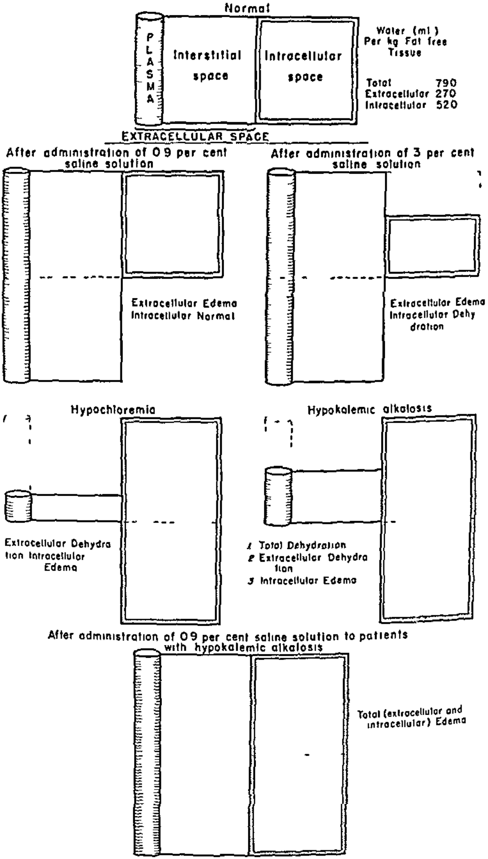


Fig 9 5 The normal content and distribution of muscle water contrasted with defects in quantity and distribution of water produced by various conditions observed in the surgical patient

cells are sometimes profound and when it is recalled that corrections are attempted by depositing repair solutions in the extracellular compartment (plasma ingestion, or hypo dermoclysis) the importance of appreciating tude of the electrolytic changes are offered by analyzing muscle for its total water and electrolyte content

If a segment of muscle be dried to con stant weight the difference from its original

TABLE 9 6 —Daily Quantity Per 24 Hours and Electrolyte Content of Body Secretions

	Quantity ml per 24 hrs	*Na mEq /l*	*K mEq /l*	*CL mEq /l*	*mEq /l*
Saliva	1500	10	25	10	10
Gastric juice	2500	60	10	85	10
Bile	500	150	5 0	100	40
Pancreatic juice	700	140	5	75	120
Intestinal juice	3000	110	5	105	30
Ileostomy	?	130	10	115	
Cecostomy	?	50	10	40	
Stool	300	50	50	75	

Expressed in round numbers because the range can be very great

the transfer relationships across the cell boundary becomes manifest

The type of fluid lost depends upon the source of the loss and reference to Table 9 6 will show the concentration of various electro lytes of different body secretions It is essential to define these electrolyte losses associated with the fluid losses and to replace them as indicated

ABNORMALITIES OF ELECTROLYTES IN SURGICAL PATIENTS

The withdrawal of gastric juice from hu mans results in metabolic alterations that affect the entire fluid and electrolyte structure of the organism The results of withdrawing gastric juice from patients with gastric cancer (anacidity) will be presented and compared with those changes which occur in patients with gastric hyperacidity

These will serve as examples of the chain reaction of metabolic alterations that may occur from a simple primary derangement Recognition and treatment of the defects early will prevent a host of complex metabolic dis ruptions from occurring which if uncorrected in turn present complicated problems for correction

Indexes showing the direction and magni weight will present a good index of its water content An estimation of the chloride content would then permit an appraisal of the ex tracellular compartment of this piece of muscle The intracellular water and electrolyte content could then be determined The follow ing formula devised by Yannet and Darrow to permit the calculation of the compartmental partition was utilized in this analysis

In these equations subscripts ser e and i refer to serum extracellular and intracellular phases respectively [ ] refers to concentration and ( ) to total amount expressed in mM mEq or Gm

$$\frac{[Cl]_{er}}{[H\ O]_{er} \times 0\ 95} = [Cl]_e$$

$$\frac{[Na]_e \times 0\ 95}{[H\ O]_{se}} = [Na]_o$$

$$[K] = [K]_e$$

Muscle per 100 Gm fat free solids (FFS)

$$(H_2O)_e \text{ in Gm} = \frac{(Cl - 1)}{[Cl]}$$

$$(Na) \text{ in mM} = (H\ O) \times [Na]$$

$$(Na)_i \text{ in mM} = (Na) - (Na)_e$$

Summary of Composition of Gastric Aspirate as It Affects Metabolic Alterations

The essential changes between the two groups of patients depend upon the sodium content of the gastric aspirate In patients deficiency and the corresponding shrinkage of the organism s water volume Because there is a simultaneous loss of electrolytes and water rather severe defects may develop before they will be reflected by changes in the crystalloid concentration of the plasma If sodium and

GASTRIC ASPIRATION

EFFECTS OF GASTRIC COMPOSITION UPON PLASMA ELECTROLYTE CONTENT

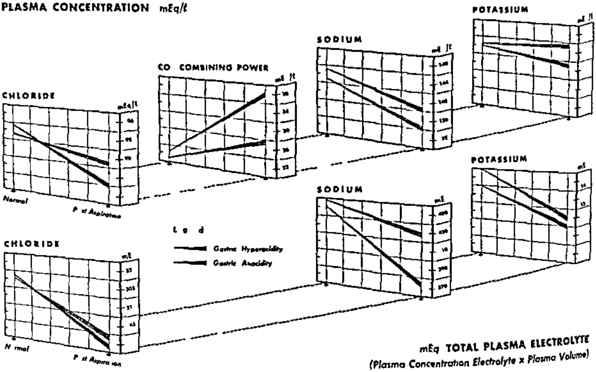


Fig 9-6 (From Ariel [6] courtesy Surgery Gynecology and Obstetrics)

with gastric hyperacidity the loss of chloride in excess of sodium produces a series of changes that consist of hypochloremia alkalosis and decrease in total body water with the interstitial space making the greatest con tribution to this loss The hypochloremia and resultant alkalosis are a strong stimulus to the development of potassium deficiency which in turn converts the hypochloremic alkalosis to a hypokalemic alkalosis In the muscle biopsies a rather significant increase in the intracellular sodium occurs apparently the result of the autoregulatory mechanism in response to the potassium deficiency and metabolic alkalosis

In contrast the essential changes produced in patients with gastric anacidity consist of total loss of sodium chloride and water This loss of a complete salt produces an electrolyte chloride were removed in equal quantities electrolyte neutrality would be maintained and there would be no compensatory mechanisms retaining carbon dioxide with the resultant production of metabolic alkalosis This oc casionally occurs and patients may lose large quantities of gastric contents with very little increase in plasma and carbon dioxide combin ing power However since there is usually some excess of chloride over sodium within the gastric aspirate a variable retention of carbon dioxide will occur and the degree of alkalosis produced will depend essentially upon the chloride sodium differential of the gastric juice

Early in the course of gastric aspiration correction of hypochloremic alkalosis can be effected by administration of sodium chloride solution However if the defect be permitted

to progress hypokalemic alkalosis supervenes and correction can only be effected by potassium administration. Chloride solution in such instances aggravates the defect.

This example exhibits a frequent surgical complication that produces fluid and electrolyte abnormalities. Diarrhea tends to produce dehydration and acidosis. Abnormalities of pulmonary mechanisms result in respiratory acidosis and alkalosis.

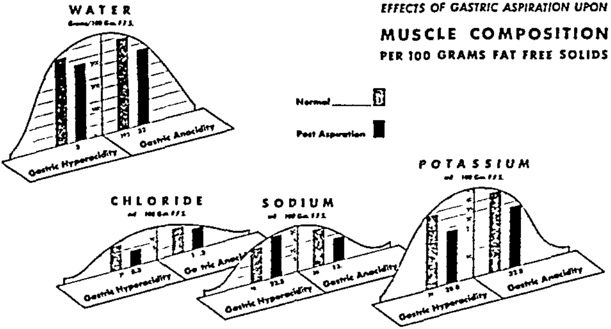


Fig. 9-7 (From Ariel [6], courtesy Surgery, Gynecology and Obstetrics.)

RENAL FUNCTION IN SURGICAL PATIENTS

Normal Kidney Function

Three major functions of the kidney are (1) excretion of waste, (2) maintenance of the acid base balance, and (3) maintenance of normal osmotic pressure.

The large quantities of water and solutes reabsorbed from the kidneys back into the circulation are indicated in Table 9-7. The kidneys function with remarkably delicate flexibility with the expenditure of tremendous energy. (The kidneys move almost 400 pounds of water and almost 3 pounds of salt per day.) However, certain shortcomings of the normal kidney exist, for example, although it can distinguish between abnormalities of acid base balance or change in the osmolar concentration of body fluid, apparently it cannot distinguish between isotonic increases in hydration. Thus an enormous increase in the extracellular space may occur but it cannot be identified by the kidney, hence no action is taken to correct it.

If the kidney can concentrate to a specific gravity of 1.030, about 600 ml. of urine will be necessary to dissolve and excrete the average of 35 Gm. of solid waste. Thus 600 ml. is the minimum of urine to be excreted per 24 hours. At urine specific gravity of 1.010, about 1500 ml. of urine is necessary to effect the excretion. Under normal conditions ingested water exerts a diuretic stimulus and is immediately excreted. Salt solutions, however, lag in their excretory pattern and there is a delay of approximately four hours before they are excreted. The normal kidney can handle practically any load given it, but in the sick surgical patient with a deranged endocrine system and possibly with direct damage to the kidney, abnormal loads in the form of improperly selected repair solutions may lead to disaster.

The remarkable ability of the kidneys to maintain normalcy should so humble the surgeon that he would try to utilize normal renal function when possible rather than attempt to substitute his knowledge (or lack of it) to accomplish kidney function (artificial kidney, etc.). It is beyond the scope of this

chapter to discuss this complex problem but suffice it to state that every effort be made to evaluate the degree of renal function and preserve it One cause of renal dysfunction in the surgical patient is electrolyte abnormalities given during the operation and during the postoperative period Such factors as anesthesia the trauma of operation per se and the body's reaction to the operation each contributes a part in the over all picture of the

TABLE 9 7—KIDNEY REGULATION OF WATER AND SOLUTES
(*After* Gamble)

	Delivered to the kidney (glomerular filtrate per 24 hours)	*Excreted in urine per 24 hours*
Water		
ml	180 000	*1000* +
Sodium		
Gm	588	2.5
mM	25 560	111
Potassium		
Gm	35 1	2.3
mM	900	60
Chloride		
Gm	658	4 2
mM	18 540	119
Phosphate (or phosphorus)		
Gm	5 6	0 9
mM	180	30
Sulfate (or sulfur)		
Gm	2 9	0 7
mM	90	23
Solids (urea etc)		
Gm	——	35
Os		
mM		1 2

The Effects of Hypochloremia upon Kidney Function

Patients suffering from hypochloremia have depressed renal plasma flow and a decreased rate of glomerular filtration Alterations in filtration fraction are not remarkable but the secretory capacity of the tubules can also be subnormal Azotemia may supervene Correction of the hypochloremia will improve the renal status and cure the azotemia (Figure 9 8)

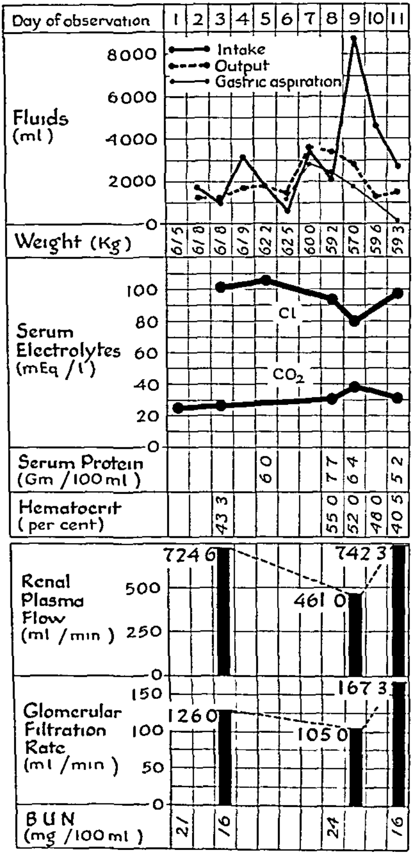
METABOLIC ALTERATIONS INDUCED BY INTRAABDOMINAL OPERATIONS

The effects of the operation upon the metabolic status of the patient will dictate the quantities and types of repair solutions to be metabolic response to the alterations incident to intraabdominal operative intervention In addition the administration of blood and other fluids during the operation further complicates the picture

Balance Between the Individual and His External Environment

There is a negative balance of water certain electrolytes and blood The quantity of water lost varies in different individuals and in different surroundings Thus in the warm summer months under heavy operative drapes the individual loses significant quantities of water (2 to 4 liters)

Contrary to the belief of many urine output continues sometimes in significant



F g 9 8 Demonstrat ng the effects of i d ced hypochlorem a on renal plasma flow and glomerula f ltrat on rate and mp aveme t of re al funct o s w th correct on of hypochlorem a (*From* A el a d M lle [8] *courtesy* Su gery)

amounts in many patients during an operative procedure and during the immediate postoperative period Although a number of individuals will manifest evidence of water retention during the immediate postoperative period this situation does not prevail for all The reason for this difference remains enigmatic

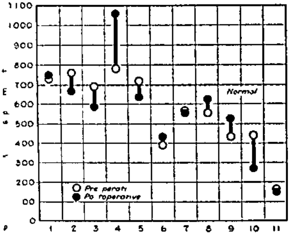


Fig 9 9 The effect of abdominal surgery upon effective renal plasma flow (From Ariel and Miller [9] courtesy Surgery)

It has been demonstrated that there is no significant kidney damage during the operation as determined by measurements of renal clearance The effects of intraabdominal operation upon the renal plasma flow are summarized in Figure 9 9 Similar results were obtained in pre and postoperative measurements of glomerular filtration and tubular absorption However if the operative trauma is great and if anoxia and hypotension occur renal damage may also occur and contribute to oliguria In most surgical patients it must be assumed that some extrarenal mechanism functions to cause water retention in those patients who receive adequate quantities of water but who retain that water postoperatively It would be erroneous to assume that water is retained by all individuals and therefore to withhold water postoperatively It would be equally erroneous to believe that for those patients who manifest evidence of water retention a greater quantity of urine can be produced by the liberal administration of water The amount of water given to an individual postoperatively should depend upon the amount lost during the operation and during the postoperative period which factor varies from individual to individual

It is difficult to measure the quantity of water lost during the operation A rough correlation exists when different methods of estimating total fluid lost are compared Total body water as measured by deuterium dilution decreased 1 2 liters in a series of patients subjected to intraabdominal operations Body weight decreased an average of 0 9 kg, a small portion of this loss was due to the resected specimen in some instances It may be assumed as a practical guide that approximately one liter of body water is lost during the three to six hours for an intraabdominal operative procedure without undue trauma

Blood Loss

There was an average loss of 300 ml of red cell mass (Table 9 8) which is equivalent to approximately 650 ml of whole blood lost or a plasma loss of 350 ml (computed on the basis of the preoperative hematocrit level)

Interstitial Fluid

Such wide fluctuations occur in the postoperative values of the interstitial spaces as measured by the sodium thiocyanate method that it must be concluded that the method is unreliable It must thus be assumed that an unknown quantity of water was lost from the interstitial spaces and the remainder from within the cells The urinary potassium lends support to this supposition as does the decrease in muscle water noted postoperatively on analysis of muscle biopsies

Electrolyte Loss During Operation

A rather close correlation exists between chloride and sodium excretion 32 mEq of chloride and 28 mEq of sodium being excreted during intraabdominal operations During this same period 16 mEq of potassium were excreted The postoperative urinary electrolytes of 67 mEq of chloride 66 mEq of sodium and 67 mEq of potassium undoubtedly represent excretory manifestations of trauma although a slight amount could conceivably be due to the 800 ml of whole blood administered during this period (Table 9 9)

TABLE 9 8 —METABOLIC ALTERATIONS INDUCED BY INTRAABDOMINAL OPERATIONS

Intake (fluids) ml				Urine (ml)			Weight (kg)		
Preoperative	During operation	Postoperative		Preoperative	During operation	Postoperative	Preoperative	Postoperative	Next A M
		Fluid	Blood						
[illegible]736	571	3399	800	575	465	1941	60 3	59 4	60 3

Total body water (D_2O) (liters)			Plasma volume (liters)			Red cell mass (liters)			Intestinal volume (liters)		
Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M
36 [illegible]	35 1	36 0	3 1	2 6	3 1	2 6	2 3	2 6	13 5	13 7	15 1

Hemoglobin (Gm per cent)			Hematocrit (per cent)			Total serum protein (Gm per cent)		
Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M
14 9	14 5	14 2	[illegible]6 3	47 6	45 3	7 0	6 6	6 6

Blood urea nitrogen (mg per cent)			Serum electrolytes mEq/l											
			Cl			CO_2 combining power			Na			K		
Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M	Preoperative	Postoperative	Next A M
[illegible]	[illegible]	11 [illegible]	[illegible] 1	[illegible]1 9	[illegible] 9	25 6	22 5	25 3	1[illegible]2 2	1[illegible]8 2	1[illegible]	4 3	4 2	4 7

There does not appear to be any correlation between the total volume of urine and the amount of electrolytes excreted It would thus appear that the excretion of electrolytes is not dependent upon the same factors that in fluence the water excretory mechanism Thus one individual may produce a great deal of ion poor urine while another may produce a small quantity of urine heavily laden with electrolytes

TABLE 9 9 —The Urinary Excretion of Electrolytes During Abdominal Operations

Chloride mEq		*Sodium mEq*		*Potassium mEq*		*Nitrogen Gm*		*K N ratio*	
During operation	*Post operative*	*During operation*	*Post operative*	*During operation*	*Post operative*	*Post operative*	*Next A M*	*Post operative*	*Next A M*
32	67	28	66	16	67	1 4	8 7	13 1	8 1

Nitrogen Excretion

Protein loss is manifested by excretion of 1 4 Gm of nitrogen during the operation, which is equivalent if all this nitrogen rep resents protoplasmic breakdown to 46 Gm of tissue (Lusk s coefficient 1 Gm N=33 Gm of whole tissue) and during the day postopera tively 8 7 Gm of nitrogen were excreted rep resenting 287 Gm of tissue destroyed if all the urinary nitrogen is the end product of tissue catabolism

All the above described alterations reflect changes between the individual and his ex ternal environment They probably represent the effects of the operative trauma upon the organism as well as a reaction of the organism to stress In addition to these changes, internal changes also occur i e alterations between the cell and its environ ment—the extracellular space—as indicated by the marked change in the total circulating plasma protein with an egress of the protein from the plasma during the operative proce dure and changes in permeability of the cell membrane to chloride and sodium in certain instances Whether any replacement therapy is indicated for these shifts is not known

The data further demonstrate the fallacy of utilizing serum concentration of various metabolites exclusively as criteria for replace ment therapy Thus a patient may lose a small amount of sodium and chloride in the urine during an operation and the immediate post operative period, but as the result of metabolic stress there may be a shift of the sodium and chloride out of the plasma into the inter stitial spaces inducing a decrease in the plasma content of these electrolytes If one is guided exclusively by concentration values of the serum one would be tempted to ad minister quantities of sodium and chloride to bring the value to normal Although the exact method of coping with this abnormal shift is not known it is believed that the excess administration of saline solution would be detrimental in such instances

Adrenal Response During Operation

The adrenal response to the stress of a surgical operation will favor the excretion of potassium and nitrogen and retention of sodium and chloride If an excessive response occurs which is further complicated by ad ministration of sodium chloride solutions abnormal retention of these electrolytes is clinically dangerous Moore and Ball have ascertained that an initial response to an opera tion (6 day period) results in the normal re lease of 875 mg cortisone 10 mg Percorten and 300 cc Eschatin Zimmerman *et al* have demonstrated the release of the powerful sodium retaining hormone androsterone fol lowing operation

Energy Expended During Operation

Other factors that must be considered in the over all appraisal of the effects of surgical intervention upon body metabolism are the quantities of energy used during an operative procedure and manifested by utilization of body carbohydrate and fat A previous study

in which the effects of operation upon liver fat and glycogen were measured by liver biopsy pre and postoperatively demonstrated an average loss of 2 Gm per cent hepatic glycogen [10] This amounted to a decrease of 45 per cent total hepatic glycogen and in some cases the hepatic glycogen decreased 50 and 75 per cent below the preoperative level There was also an increase of hepatic lipids during an intraabdominal operation sometimes to rather large amounts

THERAPEUTIC APPLICATIONS OF OBSERVED METABOLIC CHANGES DURING SURGICAL PROCEDURES

Water

The observation that an average loss of one liter of fluid occurred during operation suggests that this quantity of fluid administered during an intraabdominal operative procedure should be well tolerated The fluid loss however can be much greater especially under surgical sheets during hot summer months during which time the patients temperatures have been noted to rise to 102 to 104 (Fahrenheit) In such instances larger quantities of fluid are indicated

Blood

There is a prevalent tendency to administer too much blood during operation The most frequent guide is the patient s blood pressure and any drop regardless of cause is considered a signal for continued blood administration This is harmful and we have seen patients develop surgical polycythemia from such a practice There is no good method to determine blood volume serially during an operation hence caution must be exercised against the prevalent policy of promiscuous administration of blood A mild vasoconstrictor to combat vasodilations plasma expanders and gentle handling of tissues will reduce the necessity for administration of large quantities of blood Patients under general anesthesia do not react in the customary manner to the administration of mismatched blood Unexplained oozing from exposed surfaces may be the only manifestation that incompatible blood has been administered and should serve to alert the surgeon for further investigation of this possibility

Electrolyte Replacement

Although the loss of small amounts of electrolytes during operation should in itself not hamper convalescence it is felt that every effort should be made to maintain the preoperative balance and replacement therapy should begin at the time of operation If this be done and if certain abnormal losses occur during the postoperative period (Wangensteen suction etc) those electrolytes lost during the stress of the operation will have been replenished A dilute polyionic solution such as described by Fox *et al* and which contains 140 mEq /l of sodium 103 mEq /l of chloride 10 mEq /l of potassium 55 mEq /l of bicarbonate and small amounts of calcium and magnesium would seem to be indicated The administration of an electrolyte solution would also serve to buffer against the convulsions and coma of water intoxication that would occur if an excess of ionic free fluid were administered and retained One liter of this solution administered postoperatively would replenish the sodium and chloride losses as measured in this study The potassium decrement would not be significant provided potassium replacement were instituted within four to five days after operation

Nitrogen

The loss of 1 4 Gm of nitrogen during the operative procedure and 8 7 Gm during the immediate postoperative period is not considered clinically serious and it is felt that it does not warrant any immediate replacement therapy A healthy convalescence with oral intake of protein foodstuffs will adequately replenish this loss The plasma protein concentrations cannot be used as an index for protein replacement therapy because a large quantity of protein is mobilized out of the plasma in answer to the metabolic demands of stress In addition the hydrodynamics of the plasma will mask the true plasma protein content

Energy

The expenditure of energy with the utilization of carbohydrates and fats during an

operation demands caloric replacement The body can withstand this short period of negative energy balance provided it does not progress over a prolonged period

POSTOPERATIVE CARE

The patient immediately after an operation must be regarded as a traumatized individual in whom three sets of responses are occurring (1) those responses that are the direct result of the injury to the organism, (2) normal responses by the organism in reaction to the traumatizing actions and (3) abnormal responses due to the inability of the individual to cope with the trauma either because the trauma was too extensive and/or the individual s response mechanism is defective An example of the severe trauma is massive hemorrhage and of the defective response mechanism, Addison s disease

When a well nourished otherwise healthy individual has been subjected to a moderately traumatizing surgical procedure the immediate reactions will consist of (1) a mild fever (for which antibiotics are not indicated), probably the result of foreign protein reaction, (2) a brief period of starvation and (3) an increased catabolism which is a result of the operation The losses as described under Metabolic Alterations Induced by Intraabdominal Operations are not great and careful attention must be given to balance, avoiding the overadministration of any intravenous solution encouraging early ambulation and early active respiratory exchange Certain changes that have been unduly stressed by some investigators may occur These include oliguria or anuria an excessive excretion of potassium, retention of sodium or chloride or excessive nitrogen excretion In the authors experience these abnormalities may occur to a severe degree occasionally and must be respected when they do occur When urine excretion is suppressed except in the occasional instance it is usually transient lasting during the day of operation and the first postoperative day It is never harmful and it is considered advisable not to attempt to encourage urine excretion Administration of too much 5 per cent dextrose in distilled water to patients with transient urinary suppression will produce hypotonicity of body fluids with resultant convulsions, saline overadministration will produce edema and overadministration of blood will embarrass the cardiorespiratory system It is considered better to err on the side of underadministration because the body can cope with such a situation

Studies of the adrenal response in such patients will demonstrate a diminished amount of circulating eosinophils and an increase in the urinary 17 ketosteroids The organism can tolerate the trauma and posttraumatic period by its well integrated adaptive mechanisms A hands off policy is indicated for the first 2 to 4 days, replacing only estimated or calculated losses If the patient has not recuperated to the point of ambulation and of oral ingestion of foods by this time a program of intervention must be charted The essentials during this period are to respect the body s ability to withstand the trauma and to watch carefully for the development of any complications Blood volume must be maintained careful attention must be given to hemoglobin hematocrit and protein levels realizing that these measurements are only measurements of concentration Continued blood loss will become evident by diminishing hemoglobin and hematocrit marked water loss will be reflected by an increasing plasma protein concentration It may be mentioned that in the patient receiving antibiotics the orthodox symptoms and signs of abscess formation and peritonitis will frequently be absent and the only indexes of their presence will be a continued low gr de fever beyond the first two postoperative lays a reluctance to ambulate and hypoproteinemia due to loss of plasma proteins into the abscess These complications should of course be treated by appropriate measures

The handling of fluids and crystalloids given to patients during the immediate postoperative period will be different in many instances from that of an unoperated person It has been demonstrated that sodium chloride solutions will be distributed in the interstitial space in greater quantity and for a longer period than the same salt load given preoperatively It has been shown that normally proteins are mobilized into the plasma subsequent to a salt load in an effort to maintain

normal osmotic relationships In the post operative patient this mechanism is faulty and the saline solution diffuses into the interstitial spaces Figure 9 10 shows the plasma chloride concentration subsequent to a load of 27

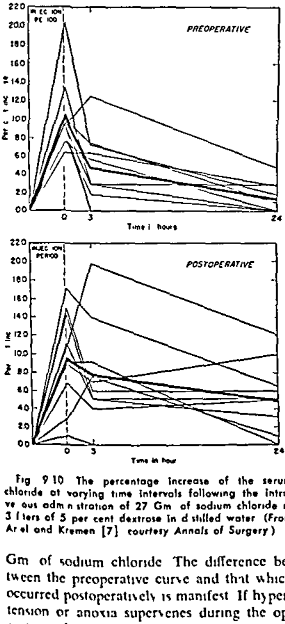


Fig 9 10 The percentage increase of the serum chloride at varying time intervals following the intravenous administration of 27 Gm of sodium chloride in 3 liters of 5 per cent dextrose in distilled water (From Ariel and Kremen [7] courtesy *Annals of Surgery*)

Gm of sodium chloride The difference between the preoperative curve and that which occurred postoperatively is manifest If hypertension or anoxia supervenes during the operation the cell members become disrupted and sodium and chloride enter the cell producing further derangements with a lowering of the plasma concentration levels of these ions

The handling of a water load to patients postoperatively depends upon their renal excretory capacity In a group of 20 patients given an intravenous water load of 3 5 liters during the immediate postoperative period 8 maintained good urinary excretory ability and 12 retained the administered water In the latter group a few presented convulsions and other signs of acute water intoxication with dilution of the various plasma crystalloids The cause for the difference of response remains an enigma but indicates that each patient must be individualized regarding his personal reaction to a water load postoperatively The effects of the water load on the plasma chloride are shown in Figure 9 11

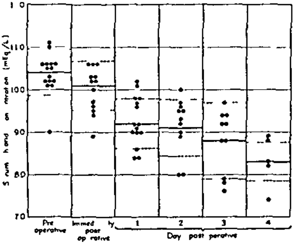


Fig 9 11 A scatter diagram of the serum chloride concentration of surgical patients who received 5 per cent dextrose in distilled water postoperatively referred to the preoperative and postoperative values The heavy unbroken line represents the mean of each day and the area between the broken lines represents the values between the plus and minus standard deviations from the mean (From Ariel [3] courtesy *A.M.A. Archives of Surgery*)

The Complicated Response

If the surgical trauma has been extensive if blood loss has been great and replacement inadequate or delayed or if anoxia has occurred during the operation the surgeon s task will be great to conduct such patients through the immediate postoperative period Some patients who have been subjected to shocking traumatization will rebound with gratifying speed In such instances a conservative therapeutic policy is indicated In others however the postoperative period is punctuated by various complications Distressing sequelae consist of prolonged oliguria or anuria with retention of nitrogen sodium and chloride and the liberation of potassium from the cells into the plasma The exact mechanism for this complication is not known but the entity lasts

TABLE 9 10 —ELECTROLYTE CONCENTRATIONS OF REPAIR SOLUTIONS COMPARED TO PLASMA

Solution	Cations (base) (mEq L)					Anions (acid) (mEq L)				
	$Na+$	$K+$	$Ca++$	$Mg++$	NH_4+	Cl	HCO_3-	Lactate	Citrate	$HPO_4=$
Plasma (average normal)	*142*	*5*	*5*	*2*		*103*	*27*	*5*		*1*
Saline isotonic (0 9%)	154					154				
Saline hypotonic (0 45%)	77					77				
Saline hypertonic (5 0%)	850					850				
Ringer s solution	147	4	6			157				
Sodium bicarbonate isotonic (1 5%)	178						178			
Sodium lactate ⅙M (1 9%)	167							167		
Saline lactate	154					103		51		
Ringer s lactate	130	4	4			111		27		
Darrow s (K lactate) solution	122	35				104		53		
Ammonium chloride ⅙M (0 9%)					167	167				
Ammonium chloride hypertonic (2%)					375	375				
Multiple electrolyte solutions										
Butler s (1946)	30	15				22		20		3
Butler s (1950)	55	23		5		45		26		12
Electrolyte No 2 in Travert (Baxter)	57	25		6		50		25		12 5
Polysal (Cutter)	140	10	5	3		103		47	8	
Special electrolyte solutions										
Gastric										
Electrolyte Solution G (Abbott)	63	17			70	150				
Electrolyte No 3 in Travert (Baxter)	63	17 5			70	150 5				
Duodenal										
Electrolyte Solution D (Abbott)	138	12				100		50		
Modified Duodenal Solution (Baxter)	80	36	4 6	2 8		63		60		
"Amino acids" 5 per cent										
Amigen (Mead Johnson)	30	15	5	2		22				23 0 3
Aminosol (Abbott)	4 3 8 7	10	1 3	0 4 0 8						23
Travamin (Baxter)	113	5 5	3 5			51				

usually from 3 to 7 days after which there is a profound diuresis with urinary excretion of electrolytes The therapy for this complication consists of a hands off policy during the period of oliguria supplying only such water as is lost A mild anemia is best left untreated because some of these patients are sensitized and will develop unexplained hemolytic reactions to administered blood The surgeon must be constantly on the alert in such instances to treat boldly by administering large quantities of electrolytes and water when diuresis ensues

The response of the malnourished weakened patient differs from that of the robust individual in many respects It may vary from failure to institute a reaction to stress such as seen in the Addisonian patient to an effective alarm reaction—but with an extreme proclivity to development of postoperative complications In such patients a preoperative test of adrenal function as advocated by Thorn may be advisable if the test indicates hypoadrenalism and an operation is nevertheless mandatory the cautious administration of cortisone during the surgical period may be indicated and a postoperative regime may be instituted similar to that utilized for patients after adrenalectomy

In those malnourished individuals who had been prepared for operation by an intensive preoperative regime with the aid of surgical intervention (gastrostomy enterostomy for feeding, etc), it has been the authors experience that the nutritional status is sometimes more apparent than real and the bottom drops out after operation with the development of hypoproteinemia poor wound healing increased susceptibility to infection delay in development of peristalsis with resultant gastrointestinal distention etc In such patients it is advisable to push nutrients by every means possible avoid overhydration and excess electrolyte administration keep alerted to the development of any complication e g hypochloremia and correct it instantly before the chain reaction of metabolic disturbances develops

It is essential to measure all losses from the body (vomiting Wangensteen suction, diarrhea exudates and transudates) and on the basis of their content of electrolytes and proteins to replace these volume for volume The surgeon can have a better index for replacement therapy by measuring the content and composition of body losses than measurements of chemical composition of the blood Table 9 10 presents various repair solutions available for intravenous administration

CHAPTER 10

Estimation of Operative Risk and Preoperative Preparation of the Poor-Risk Patient

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and
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GENERAL CONSIDERATIONS

Operative risk is the percentile chance of the patient to survive operative intervention It must also include an estimation of possible complications and the loss of recovery of function as a result of surgery If an organ such as one kidney or a lung is removed will there be sufficient functioning tissue or reserve remaining to carry on renal or pulmonary function? Will such removal result in failure of another system such as cardiac decompensation as a sequela of pulmonary compromise? Two thirds of postoperative deaths occur in patients fifty five years or more of age

The patient bearing so lethal a disease as cancer must of necessity be subjected to calculated risks especially those in the older age brackets who often suffer also from concomitant metabolic or degenerative diseases This chapter will discuss certain of the major diseases which influence the conduct of a patient with cancer through the surgical extirpation of the cancer and subsequent recovery

OLD AGE AND OPERATIVE RISK

Advances in medical knowledge have played a major part in the increase from 49 2 years in 1900 to 66 7 years in 1946 in the average life span and in the concomitant rise in the number of aged individuals in our population [9] Cancer is the second cause of death in the United States but the death rate per 100 000 from cancer increases from 21 in the segment of population aged twenty five to thirty four years to 700 in those sixty five to seventy four years of age Nearly 50 per cent of all cancer deaths can be accounted for among patients sixty five years and older

The treatment of cancer in the aged has been handicapped by the pessimism associated with cancer superimposed upon old ag Too often the physician has to overcome an attitude of prejudice and resistance both in family and patient to the need of major surgery to circumvent an early demise from neoplastic disease Surgical risk is often exaggerated and made to assume formidable proportions in relation to the patient of seventy years or older

Various excuses or reasons are often advanced for inadequate treatment of cancer in the aged patient and are worthy of mention (1) He hasn t long to live anyway (2) He is too old and why bother to put him throu h the ordeal of surgery (3) He is too old to stand surgery or He has heart disease etc. (4) He has cancer and you haven t much of a chance to cure that

To answer the first category of excuses reference need only be made to the fact that the patient of seventy years has an average expectancy of 9 22 years and the patient of eighty 5 27 years These years can be precious and productive

That patients of seventy years or older do survive surgery is shown in Table 10-1 where

it is seen that 26 of 161 patients so treated by the Pack Medical Group are alive and well 4 to 10 years after their operations Another 75 of the 161 patients were still alive one year or more and their expectancy is still to be deter

TABLE 10 1—SURVIVAL TIME OF PATIENTS SEVENTY YEARS OR OLDER FOLLOWED POSTOPERATIVELY FOUR OR MORE YEARS BOTH LIVING AND DEAD SUBJECTS

Operation	*No of Patients*	*Survival in Years*
Subtotal gastrectomy	2	4 6
Abdominoperineal resection	5	5 5 25 5 75 6 75 6
Carcinoma of rectum	1	7
Sigmoidectomy	4	4 50 4 50 7 75 7
Hemicolectomy	1	6
Radical mastectomy	1	6 50
Simple mastectomy	4	5 25 5 25 5 50 9 75
Carcinoma of uterus	2	5 74 10
Tumor of oropharynx	1	7 50
Jaw resection	1	6 50
Total glossectomy	1	7 25
Carcinoma of orbit	1	4 50
Carcinoma of nose	1	5 50
Hemilaryngectomy	1	5 75
	TOTAL 26	

mined A salvage rate of 62 7 per cent for a year or more cannot be put off by the oft repeated statement that the patient is too old weak sick etc to survive surgery Chronologic age per se can never be considered a contraindication to major surgery the decision depends more upon the function of the patient s vital organs and the extent to which known defects in function can be corrected

Adequate treatment of cancer in the aged is rewarded by end results almost as good as in the younger age groups [14] Let us consider these In a series of 161 aged patients (99 males 62 females) who had 188 operations of which 96 were major intraabdominal procedures performed despite serious co-existing disease there were 20 operative deaths This represents an incidence of 12 4 per cent of 161 patients or 10 5 per cent of 188 operations

Eighteen of the 20 operative deaths occurred following major abdominal surgery done for 96 patients and the remaining two after a radical mastectomy and hemiglossectomy respectively Ten of 35 patients undergoing major gastric surgery succumbed and five of 46 patients with carcinoma of the colon died accounting for 15 of the operative deaths Three succumbed after exploratory laparotomy where extensive inoperable carcinoma of the stomach was found

Of the 141 surviving surgery, 110 had no postoperative complications and 31 had single or multiple complications before leaving the hospital Since leaving the hospital 65 have died of their carcinoma and of other causes with a survival of from 4 to 48 months

PHYSIOLOGIC ASPECTS OF AGING

The effects of age upon the various organ systems is deceptive The associated disorders although neither unique nor consistently present differ considerably in degree and variety from those encountered in younger age groups In the aged disease and dysfunction of most organs and tissues are encountered in varying degree affecting the functional reserve in a way that is most difficult to assess In some instances this depletion may be serious and the reserve borderline or marginal

Decreased function in one organ may demand compensatory adjustment by other organ systems precipitating failure in chain fashion of for example the cardiac pulmonary and renal systems This interdependence of function can thus be seriously compromised by placing moderate stress upon the most vulnerable link in the physiologic mechanism eventually precipitating failure of less dam

aged organs Thus stress or increased demand anywhere along the line may precipitate general collapse

Under ordinary conditions the aged adjust slowly to handicaps by decreasing activity in proportion to available reserve The great danger inherent in this outwardly normal but deceptive appearance only becomes apparent when exhaustion of reserve is reached or when a sudden load is placed upon an organ system with marginal reserve capacity Under such circumstances a relatively minor stress might precipitate a chain reaction leading to depletion of reserve function of single or multiple organs

HEART DISEASE AND OPERATIVE RISK

Use of the classifications of heart disease of the New York Heart Association is an important aid in evaluating the risk of surgery Patients in Class III C or more are poor operative risks *Absolute cardiac contraindications to operation* include the presence of congestive heart failure acute myocardial infarction active pericarditis or myocarditis bacterial endocarditis and acute paroxysmal or uncontrolled arrhythmias

Increased risk is associated with cardiac enlargement borderline congestive failure aneurysms of the heart the presence of intracardiac thrombi aortic stenosis or insufficiency coronary disease status angionosus Adams Stokes syndrome carotid sinus syndrome pulsus alternans and paroxysmal dyspnea

On the other hand bundle branch block per se incomplete heart block hypertension well compensated valvular disease controlled arrhythmias and healed myocardial infarcts increase the operative risk but slightly [49 59, 96] It is much more important to evaluate risk in heart disease in terms of the functional therapeutic and physiologic status than in terms of any specific anatomic or electrocardiographic diagnosis

PREOPERATIVE PREPARATION OF PATIENTS WITH HEART DISEASE

Preoperative digitalization is usually indicated in any patient whose heart disease results in moderate to marked limitation of activity Digitalis leaf can be given over a 1 to 3 day period in divided doses totaling 1 3 to 2 0 Gm , followed by a maintenance dose of 0 1 Gm daily If digitoxin is given, 1 2 mg may be given initially or over a 6 to 12 hour period followed by a maintenance dose of 0 1 to 0 ? mg daily The sodium intake should be limited to 0 5 Gm per 24 hours injections of 1 to ? ml of a mercurial diuretic should be given intramuscularly once or twice during a period of 5 to 10 days

Patients with frank congestive heart failure require more vigorous and prolonged preparation Ideally, the symptoms and physical signs of heart failure should be corrected or brought to an irreducible minimum 7 to 10 days before operation If heart failure is untreated prior to operation an increase in operative mortality of 10 to 30 per cent can be anticipated Patients with marked cardiac enlargement or borderline failure are hazardous risks and should be treated preoperatively the same as the patient with frank congestive failure Every effort must be made to reduce those associated factors that increase the load of the heart and contribute to its possible failure These include among others the correction of anemia hypoproteinemia hyperthyroidism and hypervolemia

When *anemia* is corrected dyspnea precordial pain and other signs and symptoms of heart disease may clear promptly [19] In the patient with heart disease anemia should be corrected by the administration of 250 to 500 cc of washed red blood cells every 12 to 24 hours until the red blood cell mass approaches normal Acute blood loss is much more hazardous since associated tachycardia and blood pressure fall increase the work of the heart while decreasing its oxygen supply

Hypoproteinemia will accentuate edema formation in the patient with heart disease The decrease in osmotic pressure due to hypoproteinemia may be sufficient to cause edema but when the increased capillary venous pressure due to heart failure is added pulmonary edema ascites pleural effusion and massive edema may rapidly develop Protein deficiency may also be associated with incipient beriberi heart disease [39] Hypoproteinemia can sometimes be corrected (if the red cell mass is normal) by daily administration of 25 to 50 Gm of salt free albumin intravenously Replacement of protein in pa

tients with cardiovascular disease is limited by the need for salt free protein human albumin being the most effective The more available less expensive salt poor hydrolysates are an unsatisfactory compromise Edema due to hypoproteinemia is frequently impossible to correct by the administration of digitalis diuretics or by vigorous salt restriction

Hyperthyroidism may precipitate heart failure by its demand for increase in cardiac output and must be controlled preoperatively preferably with one of the antithyroid compounds

Increased blood volume and blood viscosity as seen in polycythemia may demand preoperative phlebotomy to prevent operative or post operative circulatory failure or thrombosis Excessive or rapid transfusions or infusions by suddenly increasing the blood volume may exact excessive demands on the heart and precipitate sudden failure

Any activity that suddenly demands an increase in cardiac output may precipitate heart failure These include infection sudden exertion fever prolonged cough hot humid weather and others In the last situation the use of an oxygen tent not only helps control anoxia but will provide favorable humidity and temperature

The administration of cortisone ACTH DOCA testosterone or estrogens promotes retention of salt and may precipitate heart failure

The patient who has a healed myocardial infarct tolerates major surgery surprisingly well with a mortality rate of about 6 per cent but he is subject to greatly increased respiratory complication rate [59] Digitalis and diuretics may be given preoperatively providing evidence of low cardiac reserve is present Even more important are the prevention of a fall in blood pressure during operation and meticulous attention to postoperative care A patient with acute myocardial infarction should not be subjected to any but the most emergent surgical treatment within six to eight weeks after the onset [41] Emergency operation under such circumstances is associated with a 50 per cent mortality

Angina pectoris is considered a precursor of myocardial infarction and patients with severe angina react poorly to operation Preoperative treatment consists of the administration of nitroglycerine and oxygen combined with digitalis diuretics and salt restriction when indicated The maintenance of normal blood pressure and adequate oxygenation is mandatory

Patients with aortic disease of rheumatic or syphilitic origin fall into a similar category They are particularly susceptible to a fall in blood pressure which may result in sudden and fatal decrease in aortic pressure and in coronary blood flow [77] Although perhaps less subject to auricular fibrillation they are prone to develop sudden and severe pulmonary edema Angina pectoris or coronary insufficiency frequently occurs and may be mistaken for acute infarction

The presence of *mitral disease* constitutes an increased operative risk Preoperatively digitalis, diuretics and salt restriction are instituted when the cardiac reserve is low The possibility of acute myocarditis in a patient with rheumatic heart disease exists when fever tachycardia and respiratory distress are present and major surgery, unless of an acute emergent nature is contraindicated

Marked hypertension with attacks of paroxysmal nocturnal dyspnea (in reality episodes of transient acute left heart failure) generally is an ominous combination usually associated with severely limited cardiac reserve Preoperative preparation includes digitalization a trial of the hypotensive agents rigorous salt limitation and salt depletion with mercurial diuretics as necessary A period of rest in the hospital under adequate sedation is most desirable If attacks of nocturnal dyspnea persist major operative procedures should not be performed unless the alternative to non surgical management is death or suffering

Pulsus alternans is often overlooked and almost always indicates serious myocardial disease It is commonly associated with prolonged hypertension and coronary artery disease Equally hazardous operative risks exist in patients subject to episodes of Adams Stokes syncope due to cardiac arrest or paroxysmal ventricular tachycardia Preoperatively such patients should be digitalized if the block is *not* due to digitalis and should perhaps be given atropine in doses of 0.5 to 1.0 mg every 8 hours and ephedrine sulfate 50 to 100 mg

and/or 15 to 45 mg of isopropyl norepineph rine (Isuprel) every 4 to 6 hours Quinidine should not be given to these patients Cardiac arrest should be anticipated as an operative complication and facilities should be available for cardiac massage and defibrillation Shock and anoxia are always of serious import and great danger to the patient s survival, if severe

The patient with *essential hypertension* usually tolerates major operations well with proper preoperative care

Patients with *diseases of the pericardium* unless active and inflammatory in nature can be prepared over a period of time for cardiac or other operative procedures by measures al ready described

FALLIBILITY OF TESTS FOR EVALUATING CARDIAC RISK

Of patients with coronary disease 25 to 40 per cent may have a normal resting electro-cardiogram and the history and physical find ings may be unremarkable The exercise and anoxemia tests may uncover borderline or un suspected heart disease in a significant pro portion of but by no means all individuals [83] The interdependence of respiratory renal and cardiac functions is probably re-sponsible for many unexpected cardiovascular complications since failure of one system may so often lead to embarrassment and failure of others For example anoxemia resulting from pneumonia or atelectasis or renal failure (treated with excessive administration of saline) may lead to heart failure [20] Be cause of this organ interdependence multi ple disorders enhance the risk of each single abnormality and complicate evaluation of the operative risk whether it be in terms of cardiac pulmonary renal nutritional or other classi fication

EFFECTS OF OPERATIVE TRAUMA AND ANESTHESIA UPON CARDIAC RISK

Postoperative cardiac complications are closely related to the duration magnitude and site of the operative procedure The choice and hazards of various anesthetic agents are discussed elsewhere Sympathomimetic agents increase the work of the heart dispro portionately to any associated increase in coronary blood flow and may precipitate ar rhythmias, particularly during cyclopropane anesthesia When shock does not appear to be due to blood loss or to arrhythmia the patient with heart disease can be given 2 to 4 mg of norepinephrine suspended in a solution of 250 cc of 5 per cent glucose In general blood and fluid replacement should not exceed the estimated loss and should be given at a rate of 5 to 10 ml per minute Any concentration of oxygen less than 20 per cent in the inspired air will definitely handicap the cardiac patient and should never be permitted Oxygen should be continued for three to five days after the operation

Pituitrin should not be given when pentothal is the anesthetic agent especially in patients with heart disease because of the deleterious effects of this combination on coronary blood flow and blood pressure [63] It is perhaps wise never to give parenteral pituitrin to a cardiac The positioning of the patient affects vital signs For example sudden tilting may lead to irreversible hypotension even in the normal individual [95]

CARDIAC ARREST

Cardiac arrest has responded to adequate treatment in over 50 per cent of proved in stances 'Arrest persisting for more than eight minutes is almost always fatal The use of the external cardiac pacemaker devised by Zoll can be quickly applied and may obviate the need for cardiac massage in many in stances Until the chest is opened and the heart exposed efforts to massage it through the diaphragm when the abdomen is opened should be made After exposure of the heart this organ is grasped with the thumb ante riorly cradling the left ventricle in the fingers and rhythmic massage is begun at a rate of 60 to 70 times per minute When the arrest is due to ventricular fibrillation defibrillation must be done with appropriate apparatus [10] If the heart fails to respond to massage 1 to 5 mg of epinephrine may be injected into the left ventricle but when ventricular fibrilla tion is present intracardiac injection of epi nephrine is contraindicated For this reason injection of epinephrine is not recommended unless the heart is exposed or unless electro-cardiographic evidence of the type of ab

normality is available Under favorable con ditions the heart usually resumes regular rhythmic contractions after a few minutes with restoration of blood pressure and fre quently the operation may be successfully cular and cerebral complications A cerebro-vascular accident may occasionally be the first symptom of myocardial infarction [27] Pul monary congestion affords a good culture me dium for bacteria making the lung susceptible

TABLE 10 2 —OPERATIVE SURVIVAL IN CARDIAC PATIENTS

Author No Patients % Deaths	*Rheumatic Heart Disease*	*Hypertensive Cardio vascular Disease*	*Arterio sclerotic Heart Disease*	*Myocardial Infarct*	*Angina*	*Heart Block*	*Heart Failure*	*Syphilitic Heart Disease*
Hickman 336 (2 0)*	60 (1 6)	91 (3 0)	44 (0)	8 (12 0)	3 (33)	11 (0)	30 (10)	
Barnes 10 (10)				22 (0)	3 (0)		10 (0)	
Senturia 446 (1 5)		446 (1 5)						
Brumm & Willius 257 (4 3)								
Levine 414 (6 3)	120 (2 1)	400 (1 0)	138 (4 9)	20 (40 5)	35 (7 7)		50 (17 1)	11 (9 1)
Love 78 (18)	16 (0 6)	29 (3 4)	34 (29)					
Sprague 76 (24 7)								

* Figures in parentheses indicate percentage of death

concluded Many times unfortunately the heart either fails to resume normal contrac tions or when it does the blood pressure is poorly maintained arrhythmias develop and acute congestive failure appears Even more discouraging is the patient who recovers but as a result of cerebral anoxemia exhibits per manent brain damage [103 117 118]

OPERATIVE MORTALITY FOR PATIENTS WITH HEART DISEASE

Table 10-2 emphasizes the difficulty in esti mating the operative risk in patients with heart disease and indicates that arteriosclerotic heart disease with or without infarction an gina pectoris and congestive failure may be associated with a high mortality

THE TREATMENT OF POSTOPERATIVE CARDIOVASCULAR COMPLICATIONS

Heart disease is associated with an increased incidence of pulmonary renal peripheral vas to complicating pneumonitis Diminished cardiac output leads to a striking degree of renal dysfunction and slowing of peripheral blood flow may precipitate thrombophlebitis and phlebothrombosis Concurrent dysfunc tion of other organs may adversely affect cardiac function

OXYGEN THERAPY

All poor risk patients with heart disease should be given oxygen postoperatively for one to three days Anoxia can precipitate car diac renal pulmonary and cerebral compli cations Oxygen can be supplied by mask catheter or an oxygen tent affording concen trations of from 50 to 100 per cent 30 to 40 per cent and 40 to 60 per cent respectively [109 90]

POSTOPERATIVE FLUID ADMINISTRATION

Parenteral fluids should not exceed 800 to 1 000 cc above the measurable fluid loss No

saline except for that actually needed for replacement of loss should be given in the first 24 hours Usually 0 1 to 0 5 Gm daily suffices

POSTOPERATIVE NURSING CARE

The patient should be spared any unnecessary exertion but deep breathing exercises followed by brief periods of coughing and periodic aspiration of mucus from the nasopharynx are necessary to avoid respiratory complications since the latter inevitably put an even greater strain on the heart Frequent change of position will help to prevent hydrostatic pulmonary congestion and will encourage cough Mild passive and active flexion of the feet legs thighs and arms maintains muscle tone and circulation in the extremities Unless there is marked cardiac or respiratory distress rapid thready pulse, unsteady blood pressure or cyanosis the patient with heart disease should be urged to dangle and sit up in his chair just as soon as the patient without heart disease While confined to bed the cardiac should be kept in a semierect sitting position or the entire bed should be elevated 6 to 8 inches at its head [37]

Acute pulmonary edema myocardial infarction arrhythmias and cardiac arrest are the most feared operative and postoperative cardiac emergencies If these develop during surgery operative manipulation should cease until the vital signs have been restored to normal If any evidence of anoxia is present intratracheal anesthesia should be promptly instituted and in the presence of pulmonary edema oxygen can be given under a positive pressure of 3 to 5 cm of water This positive pressure is gradually reduced to 2 cm then 1 cm and then to atmospheric pressure

Emergency treatment of acute pulmonary edema consists of the prompt administration of oxygen *under positive pressure if necessary* morphine subcutaneously in doses of 10 to 20 mg the application of tourniquets in rotation to the extremities and in the undigitalized patient the intravenous injection of 1 6 mg of lanatoside C or 0 25 mg to 0 5 mg of strophanthin Inhalation of ethyl alcohol is effective [81] An electrocardiogram should be obtained If within one to two hours marked improvement does not occur phlebotomy should be considered Seven hundred to 1 000 ml of blood should be withdrawn as rapidly as possible [35] If bronchospasm is prominent, bronchodilators can be given

Myocardial infarction is a relatively uncommon operative and postoperative complication It differs in several important respects from myocardial infarction unassociated with surgical procedures Only 30 to 40 per cent of the patients developing myocardial infarction during or after surgery complain of substernal pain Dyspnea is also rather infrequent Fifty per cent of the patients with postoperative or operative myocardial infarction develop it within a few hours to three days after the start of anesthesia Occurrence of shock intraoperatively seems to be a contributing factor The mortality varies from 40 to 66 per cent Treatment is the same as for myocardial infarction not associated with surgery with the possible exception of caution in the use of anticoagulants and includes the use of oxygen morphine 10 to 20 mg subcutaneously every 2 to 4 hours—or even intravenously—for the control of pain The control of arrhythmias and the management of congestive heart failure require immediate attention

CARDIAC ARRHYTHMIAS

Arrhythmias may complicate the preoperative operative and postoperative periods No patient with uncontrolled arrhythmia should be subjected to operative intervention Premature contractions (auricular and ventricular extra systoles) may indicate incipient heart failure and warn that more serious arrhythmias may develop during the operative and postoperative periods Preoperatively such arrhythmias can sometimes be controlled by the administration of 30 mg of phenobarbital *four times* a day If there is any evidence of lowered cardiac reserve preoperative digitalization may result in the disappearance of *such* extra systoles Quinidine once popular and still effective can be given to control frequent extra systoles If toxic reactions (tinnitus nausea vomiting diarrhea) do not occur *after* a test dose of 0 2 Gm 0 4 Gm may be given every three to four hours *When the extra systoles* are due to digitalis intoxication or fail to respond to the above measures *procaine* amide (Pronestyl) can be administered by mouth or

by vein in doses of 0 5 Gm every forty-eight hours as necessary giving not more than 100 mg per minute and discontinuing the administration of the drug if there is any blood pressure fall [104 70] When given intravenously electrocardiographic control is necessary

When frequent extra systoles appear during the operation they are usually promptly controlled by the intravenous administration of procaine amide if hypotension supervenes it can usually be controlled by the intravenous administration of norepinephrine in doses of 2 to 5 mg Nausea vomiting and diarrhea are less frequent side reactions following the administration of procaine amide Quinidine lactate may be given intramuscularly by preference or rarely intravenously in doses of 0 2 to 0 5 Gm but 30 to 45 minutes may elapse before the arrhythmia is controlled Because of occasional serious reactions to intravenous quinidine it is reserved for serious emergencies only and is then given with constant electrocardiographic control [56]

The *supraventricular paroxysmal arrhythmias* include auricular fibrillation auricular flutter auricular tachycardia and nodal tachycardia Since their treatment is similar they will be considered together The drug of choice is digitalis If digitalis has not been given previously 1 6 mg of lanatoside C (Cedilanid) may be given intravenously [102] Such medication may control the arrhythmia within a few minutes to several hours If the arrhythmia is not controlled within forty-eight hours oral intramuscular or intravenous quinidine as suggested may be tried Procaine amide (Pronestyl) does not appear to be as effective but may prove useful where the patient is already digitalized or if digitalis and quinidine fail to control the abnormal rhythm When supraventricular tachycardia occurs during surgery the operation should be suspended until the arrhythmia is controlled

Ventricular tachycardia is a dangerous cardiac complication and is usually associated with grave underlying heart disease Untreated and unchanged it leads to the death of the patient in most instances Clinically it may manifest itself only by rapid regular heart beat with the patient complaining perhaps only of palpitation moderate dyspnea and some precordial distress Usually however it is associated with severe respiratory distress blood pressure fall and other signs of circulatory collapse Exact diagnosis can only be made electrocardiographically but it may be suspected in the patient with an almost regular tachycardia of 150 to 200 per minute when there is (*a*) a changing first heart sound in the nonfibrillator, (*b*) complete failure of any change in the rate following vigorous vagal stimulation or (*c*) when there is a past history of preceding frequent ventricular extra systoles [3]

The treatment is intravenous procaine amide (Pronestyl) in dosages of 0 5 to 2 Gm given under electrocardiographic control at a rate not to exceed 100 mg per minute over a period of ten minutes to one hour Quinidine may be given as previously outlined It is generally felt that digitalis should be withheld until the arrhythmia is controlled since this drug increases myocardial irritability [55]

Supplementary care of any patient with arrhythmia should include the free administration of oxygen adequate sedation (30 to 60 mg of phenobarbital four times daily) 10 to 20 mg of morphine when necessary and salt restriction Precipitating causes such as pain injudicious infusions anoxia certain drugs marked anxiety intubation and other surgical procedures should be appreciated Thyrotoxicosis uncontrolled infection pulmonary and/or myocardial infarction are possible complicating and contributing factors If congestive heart failure develops digitalis diuretics and salt and fluid restriction should be instituted as described under the care of congestive failure

THE RESPIRATORY TRACT AND OPERATIVE RISK

Pulmonary disease usually results in a combination of ventilatory and alveolar respiratory dysfunction producing symptoms on the basis of mechanical and physiologic alterations The end result in both instances is a decrease in arterial oxygen saturation increase in carbon dioxide tension [4] and a fall in the pH of the serum compensated for in part by hyperventilation

PREOPERATIVE PREPARATION

Preoperative treatment will be considered from the point of view of the pathophysiologic abnormality Obstruction of the airway may be functional and partly reversible when due to bronchospasm secondary to allergy (asthma) emphysema chronic bronchitis, or certain drugs such as Mecholyl Bronchospasm may be manifested by asthmatic episodes wheezing dyspnea, cough or expectoration occurring together with prolonged expiratory breath sounds The prolonged expiratory phase of respiration can easily be confirmed by doing a spirogram Administration of bronchodilators may result in a 50 to 100 per cent increase in the vital capacity and maximum breathing capacity One or all of the following medications may be given to minimize bronchospasm ephedrine sulfate and phenobarbital 25 mg each 4 times daily, aminophyllin suppositories 0 5 Gm every 8 hours epinephrine in oil 1 cc of a 1 500 solution intramuscularly twice daily and for acute episodes aminophyllin, 0 25 Gm, given intravenously slowly or epinephrine 0 5 cc of a 1 1 000 solution subcutaneously Aerosal inhalation of 2 25 per cent racemic epinephrine aerosal (0 3 to 1 0 cc) is often very effective in warding off episodes of bronchospasm The latter (Vaponephrine) may be administered by vaporizing it with a hand insufflator attached to a nebulizer or by means of oxygen (4 to 6 liters per minute) flowing through the nebulizer during the inspiration when one end of a Y tube is closed to force the oxygen into the vaporizer [8]

If these drugs are not effective cortisone prednisone or prednisolone often effects dramatic improvement Cortisone may be given in doses of 25 to 50 mg orally or intramuscularly every six to eight hours Prednisone or prednisolone may be preferable since they do not accentuate as much salt retention and are given in doses of *5 to 10* mg every six to eight hours Whenever these steroids are necessary preoperatively they must be given in the postoperative period intravenously in the form of compound F in doses of 50 to 100 mg for the *first* one to three days

Should these methods fail resort to helium and oxygen under positive pressure, or ether anesthesia achieved in the usual fashion or by rectal instillation of a mixture of 40 cc of ether and 40 cc of mineral oil, which may be very effective Since bronchospasm is so common to many pulmonary diseases resort to one or more of the above measures often results in marked respiratory improvement

Obstruction of the tracheobronchial tree may result from bronchial and peribronchial fibrosis as a result of chronic lung disease and may occasionally be due to kinking of a bronchus as a result of tumor mediastinal shift or pulmonary fibrosis with contraction Although little can be done to correct such abnormalities awareness of their presence preoperatively allows one to take vigorous measures to prevent retention of secretions postoperatively Obstruction to the airway is often intraluminal as a result of inflammation (chronic bronchitis etc), mucosal edema accumulation and retention of secretions in the tracheobronchial tree foreign body, aspiration, or tumor

Bronchodilators should be given in conjunction with measures to increase coughing and expectoration including the use of postural drainage steam inhalation and, if necessary tracheal aspiration Expectorants such as ammonium chloride in doses of 1 to 4 Gm four times a day or 5 to 10 drops of a saturated solution of potassium iodide may be employed although their effectiveness is open to question Sedative cough remedies should be avoided since they not only impair the cough reflex but also depress the ciliary action [97] Such detergent solutions as Zephiran (alkyl dimethyl benzyl ammonium *chloride in aqueous* solution) or serosal[OT] (dioctyl ester of sodium sulfosuccinate) may facilitate expectoration of mucoid secretions Trypsin given by aerosal inhalation liquefies dry and bronchial secretions that are difficult to raise

Intraluminal tracheobronchial obstruction is always associated with infection of varying degree and persists until the *abnormality* is corrected Administration of antibiotics by aerosal inhalation provided by vaporization with oxygen as described in the discussion of the use of bronchodilators has not proved to be as effective as hoped but *penicillin* (calcium) may be given by this method in doses of 200 000 to 500 000 units every 3 to 4 hours

Oxytetracycline (Aureomycin) streptomycin and tetracycline (Terramycin) may be similarly administered in doses of 250 to 2,500 mg., particularly when sensitivity studies of the organism recovered from the sputum indicate greater effectiveness All such patients and especially when the temperature is elevated as a result of respiratory disease pneumonitis bronchitis or bronchiolitis should be given antibiotics parenterally as well as by aerosal administration in dosages of 300,000 units daily together with dihydrostreptomycin 1 Gm daily Alveolar edema as a result of congestive heart failure is treated as discussed in the section on cardiovascular diseases The importance of controlling obstruction and secondary infection in the tracheobronchial tree preoperatively cannot be overemphasized and any or all of the methods of treatment discussed must be vigorously employed if postoperative complications and mortality are to be kept to a minimum

Measures common to the preoperative treatment of all respiratory disease include control of infection removal of retained bronchial secretions and the use of bronchodilators to combat bronchospasm Smoking should be discontinued for two to three weeks preoperatively because of the irritative effect on the bronchial mucosa The patient should be instructed in deep breathing exercises Since pathogenic bacteria are associated with sinusitis gingivitis carious teeth and other oral infections these conditions must be controlled preoperatively to avoid spread to the lung during anesthesia and surgery and during the later postoperative periods

Chronic cor pulmonale develops as a result of chronic long standing pulmonary disease Many of these patients have such severe pulmonary dysfunction that major surgery is contraindicated but some can be improved sufficiently to withstand operation especially when the circulatory changes are reversible [61]

Treatment should be directed toward correction of any associated pulmonary infection by the administration of antibiotics together with bronchodilators preservation of the cough reflex and the like Phlebotomy is indicated when the hematocrit rises above 53 per cent or when it is possible to measure the blood volume the latter is 20 per cent more than normal Right heart failure responds to the use of digitalis and such patients should be digitalized preoperatively and given oxygen for cyanosis if it does not depress respiration Limitation of activity to avoid overexertion with resulting anoxia and scrupulous attention to prevent infection are essential to prevent recurrent right heart failure

Patients with pulmonary tuberculosis without evidence of serious ventilatory or respiratory dysfunction are in general fair operative risks Active pulmonary tuberculosis demands the same treatment as would be given regardless of the surgical procedure contemplated for the management of cancer For example pneumothorax should be maintained and specific measures such as streptomycin para aminosalicylic acid or niazide continued

Preoperative medication should be chosen with care in any patient with pulmonary disease Opiates should not be employed since they paralyze the ciliary action depress the cough reflex and may cause bronchospasm [92] Phenobarbital and amytal may be given intramuscularly in doses of 0 2 to 0 3 Gm In choosing an anesthesia it is essential to provide adequate oxygen at all times [13]

THE PREVENTION AND TREATMENT OF POSTOPERATIVE RESPIRATORY COMPLICATIONS

Much of the morbidity and mortality of major surgery can be ascribed to postoperative pulmonary complications Such complications assume major proportions in any patient with known pulmonary dysfunction due to emphysema chronic bronchitis bronchiectasis pulmonary fibrosis and thoracic cage abnormality Careful attention to any preoperative respiratory complications will significantly reduce the incidence and severity of postoperative pulmonary complications Space does not permit a discussion of individual disease entities but emphasis will be placed upon the factors that cause pulmonary complications their prevention and treatment Important measures again include those directed at maintenance of an adequate airway preservation of ciliary action and bronchoperistalsis adequate supply of oxygen and effective ventilatory function Realization of these goals

demands constant vigilance and prompt action Mechanical factors such as mucous plugs laryngospasm limited respiratory movements due to splinting of the thoracic cage from pain, and injudicious bandaging of the chest interfere with ventilation and may adversely affect carbon dioxide and oxygen exchange with resultant dyspnea orthopnea and cyanosis Abnormal respiratory gas exchange may result from (1) profusion of nonfunctioning alveoli by normal capillaries (2) profusion of normal alveoli with inadequately oxygenated blood (3) normal blood passing through diseased capillaries (4) poor gaseous diffusion across the alveolocapillary membrane or (5) inadequate oxygenation of the alveoli

Pulmonary function can be impaired by improper choice of preanesthetic and anesthetic agents

Regurgitation of gastric contents with their digestive enzymes and hydrochloric acid may result in necrosis of the pulmonary tissue secondary bacterial invasion and severe postoperative pneumonitis and atelectasis [33] When the operation is completed, the lungs should be inflated with gradually decreasing oxygen concentration and finally with atmospheric air or atelectasis may develop before the patient is returned to his room since 95 per cent oxygen will be rapidly absorbed from lung tissue that is not continuously aerated, whereas the 80 per cent nitrogen content of atmospheric air will prevent such collapse [113] Nasal pharyngeal and tracheal suction should be continued until it is known that the airways are patent before the patient returns to his bed

In the immediate and very important postoperative period every care should be exercised Frequent suction of the nasopharynx and trachea is desirable Any tendency to hypoventilation must be quickly investigated and when due to respiratory depression from anesthesia or drugs respiratory stimulants including caffeine sodium benzoate or even picrotoxin are indicated If due to accumulation of mucus in the tracheobronchial tree, the latter should be aspirated by tube or bronchoscopy if necessary when it is the result of cardiovascular complications it should be taken care of as discussed elsewhere and should the hypoventilation result from impatent airway tracheostomy should not be delayed if other measures are unsuccessful The patient should be turned frequently and encouraged to cough and analgesics should be given as sparingly as possible

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Pneumothorax is a not too infrequent complication following surgery of the head and neck region or thorax and may be an obscure cause of sudden respiratory distress Occasionally repeated aspiration of air from the pleural space will suffice but usually it is preferable to place a tube in the pleural space connected to underwater drainage which will afford protection against *tension pneumothorax*

Pleural effusion almost routinely occurs when the thorax is opened and may develop as a result of infection or heart failure Aspiration of the fluid when respiratory distress or unexplained fever occurs is indicated Occasionally the use of diuretics particularly when the effusion is due to congestive heart failure may speed the disappearance of such fluid and help prevent its recurrence All such fluid aspirated should be sent to the laboratory for studies of specific gravity cell count culture and cell types The empyema most frequently seen postoperatively is the result of operative procedures in the thorax or following pneumonitis Vigorous administration of antibiotics parenterally and intrapleurally often obviates the need for open drainage When the fluid is too thick to aspirate instillation of streptokinase streptodornase or trypsin often liquefies the exudate so that it can be easily aspirated by needle [111] Failure to control infection or increasing respiratory distress due to empyema however demands open drainage of the infected pleural cavity The management of lung abscess and pulmonary hemorrhage is outside the scope of this discussion

LIVER DISEASE AND OPERATIVE RISK

Liver disease increases operative risk and the greater the damage to the liver the greater is the operative risk Severe grades of impairment are relative contraindications to major surgical procedures and active hepatitis is an almost absolute contraindication

Because jaundice secondary to obstruction of the biliary tract is susceptible to correction by operative methods differentiation of the two becomes imperative At times such differentiation is not possible particularly if the jaundice is due to a combination of parenchymal and obstructive causes It is not our purpose to discuss the differential diagnosis of jaundice but rather to describe the method of preparing patients with liver disease for operation and to discuss the postoperative management

Parenchymal disease of the liver can be roughly estimated by the available liver function tests In general major operative procedures are contraindicated when one or more of the following is present a cephalin flocculation test of 3 plus or more bromsulphthalein retention of 35 per cent or more a serum albumin level of 2 5 Gm or less and a prothrombin time which remains elevated despite the administration of parenteral vitamin K [58] Excretion of hippuric acid of 1 5 Gm or less or excretion of more than 5 Gm of galactose is a contraindication to major operative procedures Marked elevations of serum glutamic or pyruvic oxalacetic transaminase indicate the presence of active liver cell damage and are therefore a contraindication to major surgery

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The diet should contain from 120 to 140 Gm of protein 350 to 400 Gm of carbohydrate and 100 to 175 Gm of fat The fat content of the diet may appear relatively high but diets containing less fat are unappetizing When biliary obstruction is present diarrhea may result from the feeding of fats and in such instances this type of food should be restricted or pancreatic extract (Viokase) be given Vitamin supplements should include 50 000 units of vitamin A preferably in an aqueous solution and 5 000 to 10 000 units of vitamin D Vitamin B can be administered in the form of brewer s yeast 30 to 50 Gm per day or vitamin B complex containing at least 20 mg of thiamine 100 mg of nicotinic acid

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5 mg of riboflavin 25 mg of B 12, and double the daily requirements of the other substances in the B complex with vitamin C in doses of 500 mg per day, should be given Vitamin K should be given by mouth in doses of 5 to 10 mg a day when jaundice is not present and parenterally in similar doses when jaundice is moderate or severe

The presence of liver disease often causes severe anorexia Intravenous liver extract in doses of 20 to 40 cc daily may improve the appetite The patient who cannot manage adequate oral food intake must be given parenteral supplements Glucose solutions are given preferably after meals in amounts of 200 to 300 Gm daily Amino acids in amounts of 50 to 100 Gm may be given intravenously but are not always well tolerated The diet should be relatively low in sodium chloride [72] When the serum albumin is less than 3 Gm it may be necessary to give salt poor human albumin intravenously preoperatively in doses of 25 to 50 Gm, but the expense involved is usually so great that such therapy cannot be continued long enough (10 to 14 days) to achieve the desired result Hypoproteinemia cannot be corrected in the presence of a deficiency of red blood cell mass Whole blood transfusions are therefore given until the hemoglobin hematocrit and blood volume have risen to normal

Complete bed rest is an essential part in the management of any patient with severe liver disease and every effort should be made to secure strict rest throughout the period of preoperative preparation The use of lipolytic agents such as choline or methionine has been advocated in the patient with liver disease There seems to be general agreement that these supplements should be given to patients who have evidence of fatty infiltration of the liver but it is not certain that they are helpful otherwise [42] When these substances are given they are administered in dosages of 2 Gm three times daily Adequate supplies of glucose or its precursors (300 Gm a day) are necessary not only to insure adequate glycogen storage but also to spare or conserve protein depots

Patients with liver dysfunction tolerate opiates and certain barbiturates poorly Chloral hydrate or paraldehyde together with meperidine (Demerol) in relatively small doses is preferred [98] During the operative procedure, anoxemia and shock must be prevented because even if mild in degree or short in duration they are apt to produce irreversible liver failure Blood must be available in adequate quantities with facilities for rapid administration under pressure if necessary The blood should be fresh and carefully cross matched to avoid transfusion reaction Jaundice appearing within one to three days postoperatively usually reflects hemolysis of such a degree that the liver cannot excrete the increased bile pigments Hepatic dysfunction is inherent in the briefest and the least traumatic type of major surgery It appears to be independent of the type of anesthesia [54] Because of the susceptibility of the liver to anoxemia oxygen should be administered throughout the operative period and during the first 24 to 72 hours postoperatively [45]

POSTOPERATIVE MANAGEMENT OF PATIENTS WITH LIVER DISEASE

Feedings should be begun as soon as possible and patients unable to take 100 Gm of protein orally in the postoperative period must be given 5 to 10 per cent protein hydrolysate to supply 100 Gm of amino acids together with 200 to 300 Gm of glucose each 24 hours until such time as oral intake exceeds 100 Gm of protein and 300 Gm of carbohydrate The importance of immediate parenteral feeding of the patient with liver disease cannot be overemphasized Starvation for periods of 48 to 72 hours may initiate irreversible decompensation (of the previously damaged liver) [54] Vitamin supplements (intravenously or intramuscularly) are given daily so as to supply at least 10 mg of vitamin K 500 mg of vitamin C 100 mg of thiamin 100 mg of niacinamide 50 mg of vitamin B 12 5 mg of riboflavin and 10 mg of pyridoxine Choline and methionine may be given in dosages of 3 to 6 Gm daily when fatty degeneration of the liver is known to be present Liver extract may be given intramuscularly 2 to 3 times weekly in doses of 20 to 60 units or may be given intravenously The patient is restored to the preoperative regimen of diet and medication as soon as he is able to take food and fluids by mouth Since salt excretion

is impaired by the presence of liver disease, no more than 0.5 to 1.0 Gm. of salt should be given in some instances [74].

Although the use of a high protein and high carbohydrate diet in liver disease is desirable in most patients, the protein must be restricted when severe liver dysfunction is present, since the diseased liver is unable to handle the increased ammonia (NH_4) resulting from the breakdown of the protein. When blood ammonia levels rise above 3–4 mcg., coma usually ensues. By the same token, ammonium chloride should not be given to patients with significant liver dysfunction. Treatment of liver coma associated with elevated blood ammonia levels includes strict limitation of protein intake, the use of cathartics and colonic irrigation to prevent intestinal absorption of ammonia, and the giving of Neomycin 3 Gm. daily or Sulfasuxidine 5–10 Gm. daily to prevent the formation of ammonia by the intestinal bacteria. Sodium glutamate intravenously in doses of 20 to as much as 120 Gm. daily has been found useful by some investigators in the treatment of liver coma.

TREATMENT OF PATIENTS WITH DIABETES

PREOPERATIVE TREATMENT

The presence of well controlled diabetes should not *per se* increase the operative risk [28, 86]. Joslin [71] reports that the operative mortality has fallen from 11.5 per cent between 1923 and 1926 to 2.2 per cent from 1942 to 1946. The increased risk for patients with diabetes mellitus largely depends upon the associated degenerative changes secondary to generalized arteriosclerosis. Such changes also occur in young diabetic patients, being proportional to the severity and duration of the diabetes [7]. In a series of 249 patients with diabetes of 15 to 20 years duration, with an average age of onset at twelve, significant complications were: (1) arteriosclerosis in 108 of 154 cases (70 per cent), (2) retinal hemorrhage in 51 of 79 cases (65 per cent), (3) hypertension in 49 of 125 cases (40 per cent), and (4) albuminuria in 46 of 138 cases (35 per cent). The incidence of fatal disease of the coronary arteries in diabetics is twice that in the nondiabetic male population and triple that in the nondiabetic female population [26].

Ideally, any patient with diabetes should go to the operating room well hydrated, free of acidosis, and with his liver well stocked with glycogen.

Preoperatively, the patient with diabetes is placed on a diet containing 150 to 200 Gm. of carbohydrate, 100 to 120 Gm. of protein, and 50 to 100 Gm. of fat. If the patient is taking one of the long acting insulins, it is discontinued and regular insulin is substituted. The urine is tested before each meal and at bedtime, and regular insulin is given according to the degree of glycosuria as follows: 1 plus or 2 plus (0.25 to 0.75 per cent), no insulin; 3 plus (1 to 2 per cent), 15 units; 4 plus (more than 2 per cent), 20 units. If more than 80 units of insulin are needed for 24 hours (this is rarely observed), preoperative observations will indicate the amounts of regular insulin that can be given in four doses each 24 hours, with additional insulin according to the glycosuria observed.

If parenteral glucose is given, 1 unit of regular insulin for each 2 to 5 Gm. of glucose so administered is added to the infusion. For further reassurance, spot checks for urinary ketone together with estimations of the blood chemical values are indicated. With a 4 plus glycosuria and the persistent presence of ketonuria, 40 units of insulin may be given every two to four hours for as long as the abnormality persists. Occasionally, in insulin resistant patients, tremendous doses of insulin are necessary. Not infrequently, detailed information relative to electrolyte balance and blood volume must be available to insure effective control of severe diabetes.

The presence of infection almost always increases the insulin need of the diabetic by lowering his glucose tolerance and may make the management of his diabetes a difficult problem.

Persistent and progressive ketonuria is perhaps the most dependable sign of incipient diabetic coma. Occasionally ketonuria can be due to such other causes as starvation, vomiting, or diarrhea, or can be falsely positive owing to salicylates, but when associated with any abnormality of the CO combining power it demands the immediate administration of

insulin and also needed fluid and electrolytes

The patient with diabetes is usually more susceptible to abnormalities of potassium balance than the nondiabetic When a diabetic develops acidosis there is a loss of potassium from the cells into the serum At this time the potassium level may be high Following the administration of insulin however, there is a rapid diuresis of potassium and dangerously low values are likely to develop Administration of saline or insulin both cause potassium diuresis and for this reason great care should be given to adequate control of this electrolyte in the diabetic

OPERATIVE AND POSTOPERATIVE TREATMENT OF THE DIABETIC

Anesthesia and/or surgery may evoke a stress reaction which is similar to that seen following the administration of ACTH or cortisone resulting in an increase in the insulin needs of the patient with diabetes

During the surgical procedure, 5 per cent glucose and water are given intravenously with or without added insulin In the postoperative period the urine should be checked every two hours until it is sugar and acetone free If acetone is present postoperatively 25 units of regular insulin may be given subcutaneously every one half to one hour until the urine is acetone free If no acetone is present but glucose is found in the urine regular insulin is given as follows 1 to 2 plus glycosuria none 3 plus 15 units 4 plus 20 units Once the urine is sugar free it need be tested only four times daily with regular insulin being administered as described Until the patient regains consciousness or until 24 hours after the surgical procedure intravenous glucose is not given unless covered by insulin in a ratio of 1 unit for every 3 to 5 Gm of glucose so given If lactose is substituted for glucose no insulin need be added Lactose has proved useful in the control of ketonemia

It should be remembered that hypoglycemia during surgery or in the recovery period is just as dangerous as acidosis and if there is any suspicion of an overdosage of insulin no time should be lost in giving 50 cc of 50 per cent glucose intravenously

Increased insulin dosage in the postoperative period is often necessary because of associated postoperative infection intestinal obstruction, or other complications Under such circumstances the presence of acetonuria is perhaps a better guide than glycosuria

As soon as the patient can take fluid and nourishment by mouth, he is given gradually increasing diet containing 100 to 200 Gm of carbohydrate 100 to 120 Gm of protein and 60 to 100 Gm of fat When the insulin requirement has become relatively constant, longer acting insulins such as protamine zinc or mixture of regular and protamine or NPH insulin, may be started The dosage for the longer acting insulin is usually 75 to 85 per cent of the amount of regular insulin needed and is conveniently given before breakfast

In the postoperative period the patient with diabetes is subject to myocardial infarction and other vascular accidents particularly those of the central nervous system and peripheral vessels These can be combated by preventing shock and maintaining adequate blood volume and fluid and electrolyte balance Diabetics are very susceptible to pressure necrosis of the skin and need expert nursing care with frequent turning Infusions should not be given in the legs The use of tourniquets is strictly contraindicated Vasoconstrictor drugs may also precipitate gangrene Renal infection may be a serious problem and in the diabetic necrotizing papillitis not infrequently develops with uncontrolled urinary infection Antibiotics should be promptly and liberally given A diabetic demands exact attention to his fluid and electrolyte balance and fluid losses through diarrhea vomiting nasal suction fistulas and the like must be rapidly and quantitatively replaced

RENAL DISEASE AND OPERATIVE RISK

PREOPERATIVE MANAGEMENT OF THE POOR RISK PATIENT

The operative risk is affected by kidney disease in direct proportion to the decrease in kidney function Significant renal failure may be present when the routine urinalysis is essentially within normal limits except for a low specific gravity If examination of the urine shows gross abnormalities or if the urea nitrogen is elevated other function tests are necessary to evaluate the extent and cause of kidney damage Concentration and dilution tests are a rough measure of the function of

the distal tubules of the kidney Table 10 3 lists some of the renal function tests with the normal levels The starred specific measurements can be easily done in most laboratories

Prerenal deviation of fluid may result from abnormal loss of water and electrolytes as a result of *vomiting or diarrhea* There may be considerable elevation of the blood urea nitrogen together with abnormal kidney function measurements [69] Restoration of depleted fluid and electrolytes and of blood volume often results in return to normal of kidney function

Major operations for cancer might be contraindicated or associated with severe risk if for example the urinary concentration is persistently 1 010 or lower the blood urea nitrogen 50 mg per cent or more PSP excretion 25 per cent or less the urea clearance 10 per cent or less the creatinine clearance 40 per cent or less and the inulin clearance below 50 per cent

Cystoscopy and intravenous or retrograde pyelograms may uncover physical obstructions to the urinary flow if these can be corrected and the associated infection controlled adequate renal function can usually be established

Renal dysfunction due to peripheral circulatory failure from such causes as shock, hemorrhage dehydration fluid and electrolyte imbalance or reduced blood volume is often reversible

Renal dysfunction associated with congestive heart failure is poorly understood but the renal blood flow is probably reduced more than the glomerular filtration rate [53] Restoration of renal function usually follows the re-establishment of compensation

In *Addison s disease* it is important not only to correct the diminished blood volume but also to supply adequate amounts of cortisone

In renal dysfunction due to kidney disease it is important to supply adequate fluids and electrolytes to maintain the optimal level of kidney function The distal tubules of dis

TABLE 10 3 —NORMAL VALUES OF RENAL FUNCTION TESTS

Test	*Normal values*
Blood creatinine concentration*	1 to 2 mg per 100 ml
Blood NPN concentration*	27 8 to 39 4 mg per 100 ml
Blood urea nitrogen concentration*	8 9 to 15 2 mg per 100 ml
Diodrast (or hippuran) clearance (renal blood flow)	520 to 1560 ml of plasma cleared per minute
Fishberg concentration*	Specific gravity 1 022
*Fishberg dilution**	*1200 ml of urine specific gravity 1 002 voided in* 3 hours
Fractional PSP excretion*	28 to 51 per cent dye in first specimen
Inulin (or mannitol) clearance	120 to 130 ml of plasma cleared per minute
PSP excretion*	40 to 60 per cent of dye in first specimen 20 to 25 per cent in second
Serum inorganic phosphorus* concentration	3 2 to 4 3 mg per 100 ml
Tubular excretory mass index (Diodrast)	36 to 72 mg of Diodrast iodine per minute
Urea clearance	Maximal 75 ml of blood cleared per minute (100 per cent) Standard 54 ml of blood cleared per minute (100 per cent) Average normal function 80 to 120 per cent

eased kidneys often cannot conserve base by the formation of ammonia or by the excretion of an acid urine In such instances sodium must be administered in increasing amounts for combination with phosphates sulfates organic acids etc Unfortunately, excessive administration of saline may result in pulmonary edema and too little in uremia and acidosis Frequent measures of electrolytes and correction of discovered abnormalities are essential

Sympathomimetic drugs morphine Demerol and cholinergic drugs may precipitate urinary retention Mecholyl bromide and bethanecol chloride may help correct urinary retention due to reflex changes but they accentuate bronchospasm

The presence of acute or active glomerulonephritis represents a contraindication to major operations except of emergent nature since surgical procedures may precipitate acute renal failure heart failure or both The nephrotic syndrome (probably a form of subacute or chronic glomerulonephritis) makes major surgical procedures hazardous Arteriolosclerotic nephritis due to essential hypertension (nephrosclerosis) unless associated with moderate or severe renal dysfunction increases the operative risk but slightly

PREOPERATIVE PREPARATION OF THE POOR RISK PATIENT

Ideally the urea nitrogen should not be elevated and the urinary output should be between 1 200 and 2 000 cc per 24 hours Electrolyte balance should be essentially normal Anemia should be corrected preoperatively If despite all measures directed at the restoration of relatively normal renal function the blood urea nitrogen remains elevated above 40 mg per cent and the other renal function tests show evidence of moderately severe dysfunction major surgical procedures are done with the expectation of marked increases in risk

MANAGEMENT OF POOR RISK PATIENTS DURING OPERATION

In the presence of renal dysfunction drugs ordinarily excreted by the kidneys (barbiturates) should be administered with great caution

More important than the choice of anesthetic agent is the maintenance of blood pressure and blood volume throughout the surgical procedure Renal blood flow glomerular filtration and tubular function are profoundly altered by shock [112] The patient with renal disease often has an associated lowered cardiac reserve and injudicious infusions and transfusions may precipitate cardiac failure If the anesthetic and surgical periods pass without any great change in the pulse blood pressure and blood volume the kidneys can be said to have been protected insofar as is possible

POSTOPERATIVE MANAGEMENT OF PATIENTS

The development of uremia with acidosis demands a careful balance between the fluid and electrolyte needs and the capacity of the cardiovascular bed to handle the volume so administered Large amounts of electrolyte solutions are often necessary to correct uremia and associated electrolyte abnormalities The development of rales peripheral edema or elevation of the venous pressure is warning of excessive administration of water and salt Normally salt loss varies from 2 to 5 Gm per 24 hours and amounts in excess of this unless a deficiency is present may be harmful A low protein high carbohydrate diet is desirable the former decreasing the work of the kidney and the latter conserving protein stores

The patient with uremia may have in addition to an elevation of the blood urea nitrogen an increase in the phosphate levels depression of calcium and elevation of the blood chloride with a low blood sodium and usually a high potassium Potassium intake should usually be cut to a minimum making special efforts to avoid the forcing of large amounts of fruit juices Oliguria persisting for two to three days in a patient with chronic renal disease may result in irreversible uremia [78]

Ideally the daily urine output should be maintained between 1 200 and 1 800 cc and ordinarily once the kidney begins to excrete urine of normal composition the associated uremia clears rapidly

Less common postoperative renal complications include glomerulonephritis *cortical* ab

scesses or renal infarction Necrotizing renal papillitis is an occasional undetected cause of uremia and death which should be suspected in any diabetic with urinary obstruction who develops progressive uremia postoperatively

MISCELLANEOUS PROBLEMS IN THE PREOPERATIVE AND POSTOPERATIVE CARE OF PATIENTS WITH CANCER

HYPERTHYROIDISM

Uncontrolled hyperthyroidism is a contraindication to major operative procedures Medical management through the use of one of the antithyroid compounds is preferred Propylthiouracil in dosages of 150 to 300 mg three times daily will usually bring the increased metabolism under control within a period of three to six weeks Toxic leukopenia or agranulocytosis is at times a complication *Iodine in the form of saturated solution of potassium iodide* should always be given one *to two weeks preoperatively in order to prevent* excessive bleeding during thyroidectomy Tapazole (methimazole) is apparently 5 to 10 times more potent milligram for milligram than propylthiouracil and usually brings patients with hyperthyroidism under control within two to three weeks The drug is given in dosages of 10 to 40 mg three to six times daily [68]

Unless these patients are brought into satisfactory metabolic balance with basal metabolic rates of less than plus 10 circulatory collapse thyroid storm or fatal accentuation of pre existing heart disease may develop during or after a surgical procedure Radioactive iodine requires at least four to six weeks to produce a euthyroid state [24]

MYXEDEMA

The patient with myxedema represents an equally poor operative risk [46] The diagnosis of hypothyroidism in the elderly is often difficult The finding of an increase in the blood cholesterol often warns the clinician of the possibility Vascular collapse may be sudden and mysterious if the diagnosis is missed Three to four weeks of gradually increasing dosages of thyroid extract will usually suffice to prepare such a patient for major operations Congestive heart failure due to myxedema is relatively uncommon and responds well to adequate treatment

ADDISON S DISEASE SIMMOND'S DISEASE, AND PHEOCHROMOCYTOMA

Patients with Addison s disease Simmond s disease and panhypopituitarism represent notoriously hazardous risks but operative procedures can be successfully performed by proper medical management

The patient with high blood pressure due to pheochromocytoma is a poor operative risk and requires a meticulous medical regimen to conduct him safely through an operative procedure

THE TREATMENT OF POSTOPERATIVE THROMBOPHLEBITIS AND VENOUS THROMBOSIS

Differentiation between *thrombophlebitis* and phlebothrombosis is often not possible hence they are referred to as venous thrombosis [51 65] From 1 to 2 per cent of patients subjected to major operative procedures develop this complication The incidence in patients with cancer may be somewhat higher Old age the presence of varicosities polycythemia congestive heart failure the placing of pillows beneath the knees leg infusions dressings constricting venous return prolonged immobilization vigorous use of diuretics together with the known postoperative changes in clotting phenomena all contribute to postoperative venous thrombosis

Thrombosis usually becomes evident between the fifth and tenth *postoperative days* with 50 per cent developing *on the sixth to* tenth day *25 per cent from the tenth to the* sixteenth day and 25 per cent after the sixteenth day [119]

Approximately 5 per cent of patients with *untreated venous thrombosis* have pulmonary *emboli resulting in* lung infarction untreated *the mortality* of pulmonary infarction is 15 to 20 *per cent* [119] Ninety five per cent of *such* pulmonary emboli arise from thrombosis of the deep veins of the legs [5] Anticoagulant *therapy has significantly* reduced both the incidence of pulmonary embolism and of infarction

Hemorrhage from heparin or Dicumarol may develop in 3 to *5 per cent* of the patients

so treated and is an indication for withholding anticoagulants [2] Serious bleeding occurs less frequently being observed in approximately 2 per cent of such instances When a hemorrhagic tendency becomes evident either by detection of microscopic hematuria or bleeding into the gums skin or elsewhere the drug is immediately discontinued For the hemorrhages induced by Dicumarol, transfusions of fresh plasma or whole blood and the daily intravenous administration of 75 mg of vitamin K_1 oxide until the prothrombin time approaches normal represent the proper treatment Transfusions of fresh plasma or whole blood should be given to control any hemorrhage due to heparin Antiheparin drugs such as protamine sulfate (1 5 mg of protamine neutralizes the effect of 1 mg of heparin) and toluidine blue (3 to 5 mg per kg body weight), have been advocated for control of hemorrhage resulting from the administration of heparin Such treatment is continued until the Lee White clotting time is 30 minutes or less and the prothrombin time 20 to 30 per cent of normal Then anticoagulants may be continuously readministered if indicated

Other supportive care includes the administration of antibiotics and control of any associated infection or metabolic disorder

When a contraindication to anticoagulant therapy is present ligation of the saphenous femoral or inferior vena cava is recommended [1]

Prophylactic anticoagulant therapy is not recommended except in patients who have been receiving anticoagulants preoperatively to prevent emboli recurrent myocardial infarction or cerebral thrombosis The reason for this stand depends upon the fact that the incidence of postoperative venous thrombosis is 2 per cent or less whereas the hemorrhagic complication rate of anticoagulants is 5 per cent [32]

The presence of pulmonary infarction demands in addition to the prompt use of heparin and Dicumarol the employment of other agents in seriously ill patients Morphine (10 to 20 mg every four to six hours) and atropine (0 5 to 1 0 mg every six to eight hours) are given to minimize harmful reflex constriction of the coronary and pulmonary circulation papavarine (0 1 to 0 35 Gm every six hours) to promote arterial relaxation and oxygen to combat anoxemia If right heart failure occurs digitalis is given to the undigitalized patient in the form of 1 6 mg of lanatoside C (Cedilanid) intravenously Surgical treatment of pumonary embolism is not recommended since the operative mortality far exceeds that associated with the measures just outlined

Similar anticoagulant measures are indicated when arterial embolization or thrombosis develops unless surgical removal of the clot can be effected within three to four hours The use of anticoagulants is also indicated for myocardial infarction

CHAPTER 11

Electrosurgical Treatment of Neoplastic Diseases

Grant E Ward

Electrosurgery is the application of high frequency alternating electric currents for the destruction and removal of pathologic tissue or for the hemostatic incision of normal tissue in the surgical exposure of a focus of disease

Electrosurgery occupies an important place in general surgery and the surgical specialties Adequate discussions of the indications and technics of electrosurgical currents are most suitably given in the sections dealing with specific tumors This chapter will outline the fundamental principles of electrosurgery to prepare the reader better to use electrosurgery in whatever domain he is working Space does not permit discussion of the historic development of electrosurgery

PHYSICAL PRINCIPLES

Electrosurgical currents are alternating in character and of a high frequency of oscillation (750 000 cycles or above) These currents are conducted between generator and patient by uniterminal or biterminal connections *The uniterminal connection is* made by one cable extending from the generator to the active electrode the current returning through ground or air With biterminal connections two cables are used one extending from the generator to the active electrode This large electrode makes a broad contact with a convenient spot on the body widely disseminating the current so that no sensation of heat or pain is experienced

As a general working rule uniterminal currents cause desiccation or dehydration of the tissues because the tissue temperatures developed are not sufficiently high to do more than dry the cells Biterminal currents may raise the tissue temperatures to such high degrees that the cells are actually boiled in their own juices resulting in coagulation Also biterminal currents when properly balanced to produce well localized high temperatures sever the tissues allowing for rapid cutting with varying degree of destruction on each side of the incision However by varying voltage amperage and frequency of alterations the effects of uniterminal and biterminal currents can be interchanged—that is strong uniterminal currents can coagulate and weak biterminal currents will desiccate Electrosurgical cutting is usually accomplished by biterminal connections

GENERATORS

Electrosurgical generators are of two main types one using a spark gap for the source of oscillation the second employing one or more three electrode vacuum tubes The spark gap generators create a damped current i e a current oscillating in wave chains of decreasing amplitude with a short pause after each chain By carefully reducing the width of the spark gap the wave chains are brought closer together and their amplitudes reduced The closer the wave chain and the lower the amplitude, the hotter is the current the more energy flows across the gap per unit of time and the better are its cutting qualities The higher the amplitude and the farther apart the wave chains the less energy flows per unit of time and therefore the cooler the current and the better the coagulation Also the time after each wave chain allows cooling down of the tissue and gives more time for coagulation

Vacuum tube generators produce currents

of undamped oscillations i e, a constant even amplitude of waves during the period the tube is oscillating These currents as a rule, produce better cutting than is obtainable by the spark gap generators On the other hand, vacuum tube currents of even oscilla tion allow more energy to flow at a given period of time and as a rule are hotter than the spark gap currents In order to produce good coagulation with tube currents the electrodes must be placed against the tissue before the current is turned on One advantage of spark gap currents over the vacuum tube currents is that when the active electrode is moved from place to place as in coagulating a surface there is less flashing and flaming with the damped current than with the un damped vacuum tube current Flashing sparks are apt to cause more carbonization or actual charring of the tissues and less good coagulation

Fig 11 2 Photomicrograph of incision made with cutting current from tube apparatus showing fine line destruction 10 u in thickness or less Primary union is the rule here (From Kelly and Ward [2] courtesy W B Saunders Company)

HISTOLOGIC CHANGES

The old term *fulguration* should be dis carded Fulguration currents were of a very high voltage from spark gap generators with wide gaps There was much superficial shock ing with little penetration Newer electro surgical currents now replace fulguration

1 *Desiccation* is dehydration of the tissues Microscopically the cells are shriveled

Fig 11 1 Photomicrograph showing desiccation with Oudin current Tumor cells are dehydrated elongated and shriveled with shrunken nuclei (Courtesy Journal of the American Medical Association)

and elongated without loss of structure (Figure 11-1) Electrodesiccation is pro duced by cooler (weaker) currents of the spark gap or vacuum tube variety

2 *Coagulation* is actual destruction by a hotter stronger current from a vacuum tube or spark gap generator that boils the tissue in its own juices the cells being coagulated into a homogeneous mass losing all normal characteristics The parenchymal cells form granular masses while the stroma appears hyalinized with here and there remnants of coagulated blood vessels and their contained blood

3 *Electrosurgical cutting (electrotomy—Blech)* is produced by a carefully balanced high frequency electric current generated for the purpose The cutting is caused by the cur rent and not by the type of electrodes By careful adjustment of the generating appa ratus currents can be made to cut with only a tenth of a millimeter of destruction on each side of the incision Such slight tissue changes allow primary union in a high percentage of incisions (Figure 11 2) It has been shown that these scars are weaker than the scars of ordinary scalpel surgery The real clinical value of such delicate electrosurgical cutting (fine electrotomy) is questionable

4 *Electrosurgical cutting with deeper*

destruction (coagulating electrotomy) on each side of the incision (1 to 2 mm) is of value in removing cancers from vascular regions Capillaries small blood vessels and lymphatics are sealed These currents are pro-

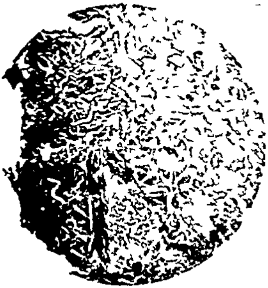


Fig 11-3 Photomicrograph of incision with spark gap generator showing deeper coagulation destruction (55 to 60 u) Primary union impossible and not wanted where this type of incision is necessary Blood vessels of considerable size and lymphatics are sealed and tumor cells at a distance destroyed This heavy cutting current is usually used for removing ulcerated and infected cancers (From Kelly and Ward [2] courtesy W B Saunders Company)

duced either by blending vacuum tube cutting currents with spark gap currents or by strong currents of either variety Primary union is of course out of the question but really not desired for heavy destructive currents are for the removal of extensive malignant neoplasms in places where primary closure is impossible (mouth face) or where the sterile bed may be covered as in the brain etc Occasionally the coagulated tissue left by the current may be excised with a scalpel and approximated by sutures Primary union may then be expected (Figure 11 3)

ELECTRODES

"Electrodes" designates the instruments at the end of the cable from the generator making contact with the patient and fall into two types active and inactive The inactive electrode is placed against the patient's skin at a suitable area preferably beneath the buttock or shoulder but not beneath a bony prominence It is often convenient to strap the electrode to the thigh using some form of elastic bandage or rubber tourniquet These inactive electrodes are frequently made out of sheet lead or brass mesh and covered with green soap or other lubricant to insure even and constant approximation to the skin Any irregularity might short-circuit the current causing a burn A dry towel is placed at the edge of the inactive electrode where the connection between the electrode and the cable is sufficiently prominent to cause undue pressure against the skin—again a danger of burn Active electrodes are of varying sizes and shapes and concentrate the current at the point of operation Detailed descriptions of these will be given (Figure 11-4)

NOMENCLATURE

The words *cautery* and *cauterization* are really incorrect Electrosurgical currents properly applied do not actually cauterize Unfortunately these terms are still used rather glibly to describe electrosurgical procedures

1 *Electrotomy* (Blech) describes electrosurgical cutting and may be defined as fine or coagulating depending upon the intensity of the current and the depth of penetration

2 *Electrodesiccation* is dehydration to the point of cell death

3 *Electrocoagulation* is the coagulation of tissue by a strong high frequency current that actually boils the cells in their own juices Coagulation may be superficial or deep

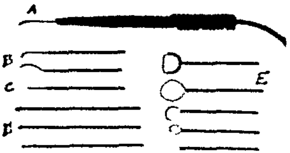


Fig 11-4 Assortment of active electrodes for electrosurgical operation A Insulated handle to hold electrode B Flat electrotomes C Needle for electrotomy desiccation or coagulation D Ball coagulators E Loop electrotomes (curettes) (From Kelly and Ward [2] courtesy W B Saunders Company)

4 *Electrotome* is an electrosurgical active electrode for electrotomy or cutting It may be made in the shape of a blade wire loop or curet, or needle

5 *Desiccator and coagulator* can be ball disc or needle shaped

6 *Electrosurgical curet* carries a high frequency electrical current to coagulate and control hemorrhage as the tumor is curetted away

7 *Electrosurgical snare* is often used to surround tumors An ordinary tonsil snare with insulated shank is satisfactory The current carrying electrotome or coagulator is touched to the snare handle the current controlling bleeding and destroying tissue as the pedicle of the tumor is cut through

8 *Electrosurgical rongeur* carries the current to coagulate the organic tissue in bone as the bone is bitten away The wire cable is attached to a binding post located on the inside of the rongeur handle

9 *Active electrode* condenses the high frequency current at the point of contact allowing for the electrosurgical effect

10 *Inactive electrode* is the wide electrode placed at a suitable spot on the skin The current is widely disseminated preventing pain or tissue destruction

SURGICAL TECHNICS AND OPERATIONS

Desiccation

Desiccation is usually accomplished by light uniterminal currents to destroy small skin lesions warts small epitheliomas and occasionally small hemangiomas (Figure 11 5) With very superficial lesions (hyperkeratoses) a light spark is sprayed over the surface A wart requires a needle to be inserted repeatedly at the proper depth (through epidermis only) at first in the moist edge and later in the center until completely surrounded and dehydrated It is then scraped off and the base re treated A mole may be circumvallated a technic described by the late William L Clark The desiccating needle is inserted repeatedly in the normal tissue at the edge of the mole and carried through all layers of the skin and into subcutaneous fat After thus blocking off lymph and blood drainage from the tumor the mole is excised Malignant moles either should be excised with a strong electrosurgical cutting or excised with a wide margin with scalpel and sutured

Coagulation

Coagulation may be accomplished by needle ball or disc coagulator In the destruction of large tumors the circumvalla

Fig 11 5 Electrodesiccation of a benign papilloma on the dorsum of the tongue In order to secure deep destruction the electrode should be inserted below the lower border of the tumor down into the muscularis (From Ward and Duff Tumors of Tongue Cyclopedia of Medicine Surgery and Specialties courtesy F A Davis Company)

tion technic is employed whenever possible The needle coagulator is inserted repeatedly around the edge of the tumor in the normal tissue remaining in each place until a ring of coagulation of one to two millimeters in width is obtained After the entire tumor is circumvallated its main mass is then attacked by either the ball disc or needle coagulator The more superficial areas can be destroyed by a ball or a disc but the deeper ones are better coagulated with the needle coagulator penetrating the desired distance The destroyed portions are curetted away and a deeper layer is attacked and so on until the entire tumor is removed Less accessible tumors located in the antrum bladder and oral cavity may not lend themselves to circumvallation and may have to be attacked directly by a suitable coagulator in repeated steps of coagulation and curettage

Electrosurgical Aspiration

Many surgeons use any suitable aspirator to keep the field dry as when working in the brain antrum bladder or other cavities When active bleeding is encountered the tip coagulation appears around the tip of the hemostat, the instrument is removed and another picked up to be touched with the active electrode

While applying the current the hemostat

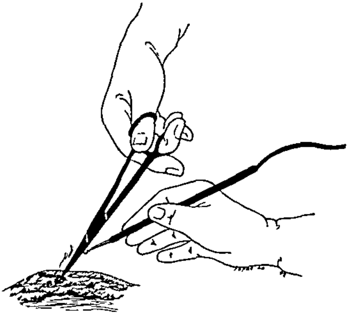


Fig 11-6 Clamp coagulation method of hemostasis Blood vessels are caught in hemostats as usual and when it is desired to bring about permanent hemostasis each clamp is picked up separately by the operator or an assistant and touched with the active electrode carrying a coagulating or strong cutting current Great care must be exercised that all blood is wiped away from the tip of the hemostat and that the hemostat does not touch nearby tissue or instruments thereby shunting the current and causing a burn or poor coagulation from dissemination of the current through a clamp (*From Ward and Hendrick Tumors of Head and Neck* courtesy Williams and Wilkins Company)

of the aspirator is pressed against the bleeding point and the active electrode applied to the aspirator Special aspirators have been made with a sterilized wire cable connected to the aspirator and the current is turned on as desired either by a switch in the aspirator handle itself or by a foot switch

Hemostasis

The hemostatic property of electrosurgical currents is one of their chief values During any surgical procedure hemostats are applied as usual When permanent hemostasis is desired the hemostats are picked up one by one and touched with the active electrode the coagulating current running down the hemostat to coagulate the vessel caught in its grip (Figure 11 6) When a small area of must not touch another instrument or any tissue except that held within its jaws as the current will be shunted away with resultant inefficient hemostasis of the vessels or a burn of normal tissue touched nearby Also all blood clots around the tip of the clamp that will disseminate the current must be removed with a sponge to limit the amount of destruction and to shorten the period of application of the current

Hemostasis is also obtained through a ball or disc coagulator These coagulators should be applied to the bleeding point before turning on the current the pressure stopping the bleeding so the current when switched on will coagulate the compressed vessel more quickly If the vessel is not first occluded the flowing blood retards coagulation allows

charring and unnecessary destruction, and interferes with hemostasis

Control of Oozing

General oozing from a vascular surface is often annoying and difficult to control by

mm), or coagulating with deeper destruction on each edge of the incision (1 to 2 mm)

Fine electrotomy for skin incision allows primary union in a high percentage of cases (85 per cent) However the scars following fine electrotomy are weaker than

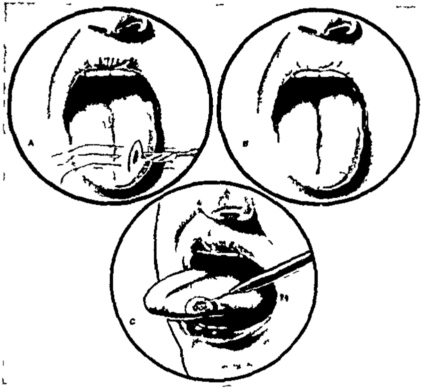


Fig 11 7 A Scalpel excision of small benign growth The black silk sutures are placed deeply in the tongue before excision of the tumor to control bleeding and facilitate quick closure B The sutures are drawn tightly and tied securing hemostasis C Electrosurgical excision of a small benign growth A small blade electrode is passed around the lesion controlling the bleeding (From Ward and Duff Tumors of Tongue in Cyclopedia of Medicine Surgery and Specialties courtesy F A Davis Company)

the direct application of a ball or disc coagulator The blood flow is so rapid that the coagulator is covered the blood is boiled and much charring results without accurate and complete hemostasis To improve the technic the oozing surface is covered with a gauge sponge under pressure The sponge is gradually moved across the oozing surface followed by a ball or disc electrode coagulating to the desired depth leaving a dry sterilized wound The coagulator controls small exposed oozing surfaces as it follows the sponge across the wound whereas it is unable to cope well with large bleeding areas

Electrotomy

Electrotomy may be fine with slight tissue damage on each edge of the incision (0 1

scars following scalpel incisions This fact plus the minimum hemostasis sealing of capillaries and small blood vessels only renders the use of fine electrotomy of questionable clinical value for skin incisions Occasionally fine electrotomy is helpful in dissecting between adherent loops of intestines leaving the thin coating of coagulated tissue to delay the reformation of adhesions Also there is less bleeding when dissecting such adherent intestinal loops making for a cleaner operation Rapid movement of the electrotome reduces time for excessive tissue destruction in fine electrotomy (Figure 11 7)

Coagulating electrotomy is of inestimable value in removing tumors from vascular and wet fields as the mouth brain urinary bladder etc and often in dissecting skin flaps

in neck and breast operations The strength of the current is regulated to produce any desired depth of coagulation from a fraction of one millimeter to two millimeters as demanded by the vascularity and type of tissue encountered Fascia of the neck with little rent is necessary to cut well In vascular fields as the oral cavity a strong current is also required to coagulate all but large (1 mm) vessels while cutting (Figure 11 8) Vessels larger than about 1 mm in diameter are clamped and coagulated Coagulating elec

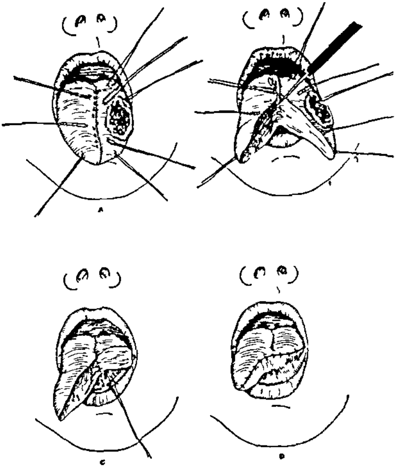


Fig 11 8 Technic of simple hemiglossectomy A Dotted line represents line of incision Two stay sutures of medium black silk are placed one on each side of the midline for traction Other stay sutures are distributed along each side of the line of incision Those on the side of the tumor serve as traction while removing the diseased tissue obviating handling with forceps a cumbersome and space-consuming maneuver in the mouth The stay sutures beyond the line of incision serve to control at all times the remaining portion of the tongue of great assistance in stopping hemorrhage B Incision with electrotome C Dotted line in floor of mouth represents extension of the incision in case the floor of the mouth is to be removed along with the primary tumor D Closure of wound with black silk or fine chromic catgut interrupted sutures This is not always possible when the floor of the mouth is removed along with hemiglossectomy (*From* Ward and Hendrick *Tumors of Head and Neck* courtesy Williams and Wilkins Company)

fat is easily severed with a weaker current than the fascia of the breast heavily laden with fat The fat melts under the heat of the current the fluid fat disseminating the current and reducing cutting properties To offset this dissemination of energy a strong current trotomy leaves a relatively dry sterilized surface as the incision is made Further coagulation and sterilization are accomplished by going over the wound with a ball or disc coagulator Slow deliberate movement of the electrotome allows time for the desired tissue

destruction in coagulating electrotomy In performing fine or coagulating electrotomy the electrotome must not be pressed against the tissue as with a scalpel Pressure against the tissue obliterates the arc necessary for cutting A tiny arc between the electrotome and tissue must be maintained at all times for satisfactory results

POSTOPERATIVE CARE

The postoperative care of electrosurgical *wounds is important For a minor electro-*desiccated area the care is rather simple Desiccation or coagulation of small lesions on the surface leaves a dry sterile coating to be treated like any other small burn An acetone alcohol solution of gentian violet 2 per cent (Bohlman) suffices to form a firm crust or scab that comes away in 2 to 4 weeks depending upon the depth of the destruction Should any infection develop beneath this scab the scab is removed and the area treated appropriately Usually however, these small lesions heal beneath the scab so that when it comes off there is almost complete healing

If the electrosurgical procedures are carried on deep in the body and the wound is closed per primum healing is to be expected and the care of patient and wound is the same as following any other operative procedure Special attention is needed where wounds are of necessity allowed to granulate or where there is extensive destruction about the head and neck interfering with the intake of food and fluids and perhaps with normal respiration Every possible precaution should be taken to keep infection of these sloughing and granulating regions at a minimum Antibiotics parenterally orally or locally are of great advantage

Good antiseptic dressings applied at the operating table are allowed to remain up to several days depending upon the circumstances If there is drainage from the oral cavity the dressings should be changed frequently either daily or several times a day

Large defects in the oral cavity are kept clean by packing with iodoform gauze changed after appropriate intervals Copious oral douches of warm saline solution make the patient more comfortable and bring away debris as it loosens

HEALING OF ELECTROSURGICAL WOUNDS

Except when fine cutting currents have been used in the skin, rarely do surface electrosurgical wounds heal per primum The superficial wounds of electrodesiccation of small skin lesions require from two to four weeks to heal beneath the created scab The *scars are soft and pliable, pink at first later* fading out and usually becoming only slightly noticeable The amount of deformity depends entirely upon the depth to which the tissues have been destroyed The superficial lesions limited entirely to the epidermis such as hyperkeratoses and warts, heal about like any other second degree burn Moles and epitheliomas requiring destruction of all layers of the skin down through the dermis leave a slightly deeper pit or a little thicker scar, should there be a tendency to keloid formation Keloids are rarely a problem

In the larger electrosurgical wounds, healing is slower and by secondary intention Slough has to come away granulations develop and the wound heals by scar These scars are very soft and pliable the disfigurement being remarkably slight in comparison to the amount of tissue loss (Figure 11 9) This is particularly true about the eye Tumors of variable size from small epitheliomas and papillomas on the lid borders up to larger ones 1 or 2 cm in diameter around the eye heal without ectropion or entropion permitting good function of the eyelids The removal of malignant neoplasms from the region of the nose allows slow gradual pulling together of the skin edges which often leaves defects assuming the normal wrinkles and lines of the face and are not very disfiguring

Larger wounds about the mouth will require plastic repair (Figure 11 10) A reasonable time six months to one year should elapse to insure against recurrence Unlike the scars following heavy irradiation electrosurgical scars are vascular and soft so that plastic repair is much more easily accomplished The vascular soft tissues readily

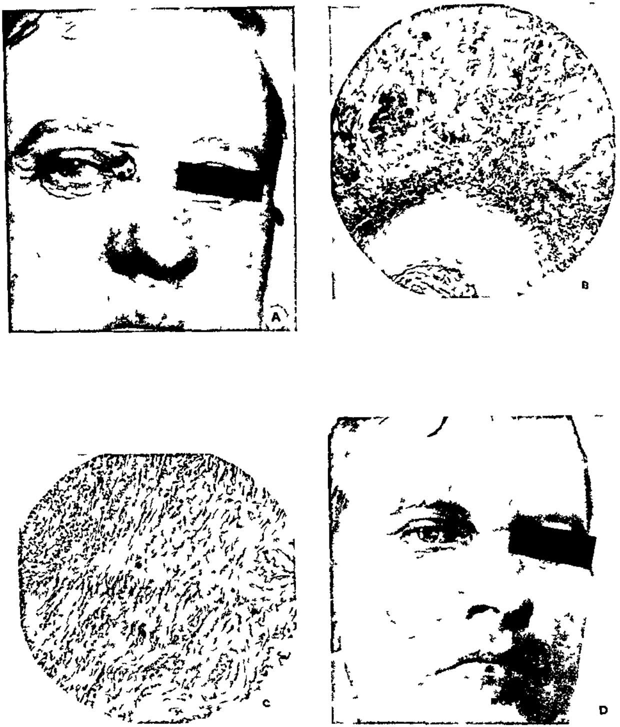


Fig 11 9 Squamous cell carcinoma persisting following irradiation A Squamous-cell carcinoma involving inner canthus of right eye Treated with x ray 2 500 r elsewhere Excised with electrosurgery care being taken to remove ramifications of tumor into orbit beside the eyeball B Photomicrograph shows persistence of tumor Epithelial cells partially destroyed by previous irradiation other cells viable Round cell infiltration Epithelial pearl C Area of tumor that was destroyed by radiation therapy showing chronic inflammation scarring obliterating endarteritis D Good cosmetic and functional results with no recurrence after five years (From Ward and Hendrick *Tumors of Head and Neck* courtesy Williams and Wilkins Company)

receive skin grafts of one kind or another after the removal of the scar itself

SUMMARY OF USES OF ELECTROSURGERY

I Electrodesiccation

A Benign lesions

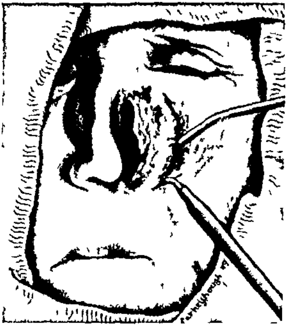


Fig 11 10 Incision with electrotome Aspirator keeps wound dry—only a few large vessels bleed and are controlled with a ball tipped coagulator (*From* Ward and Hendrick *Tumors of Head and Neck* courtesy Williams and Wilkins Company)

1 Hyperkeratosis (small area about 1 cm in diameter), larger areas are best treated by irradiation

2 Warts *

3 Lupus vulgaris

4 Papillomas and verrucae in mouth and on lips

5 Leukoplakia buccalis (thickened areas require biopsy) Ball tipped electrode used Larger areas may be treated with radium or roentgen rays through an intraoral cone

6 Condyloma about vulvae and anus Large masses may be excised with electrotome

7 Destruction of cyst walls (ranula mucous cysts of mouth cysts of Bartholin s gland etc)

* Melanomas must be surgically excised with a wide margin of tissue and when possible in continuity with lymph drainage region Plastic repair is often necessary

8 Eyes pterygia small papillomas on lids xanthoma palpebrarum

B Malignant neoplasms small basal cell epitheliomas especially about the eye lids and over cartilage of nose and ears

II Electrocoagulation

A Benign neoplasms

1 Papilloma of bladder through cystoscope

2 Rectal polyps through proctoscope

B Malignant neoplasms

1 Large basal cell epitheliomas especially about the eyes and overlying the cartilage of nose and ears These tumors may also be treated by irradiation

2 Small and large squamous cell carcinomas of skin especially after becoming resistant to radiation therapy

3 Destruction of areas of inoperable cancer in antrum or adjacent structures occasionally in mouth and urinary bladder (at operation)

4 Destruction in situ of certain inoperable brain tumors

III Electrosurgical hemostasis (clamp coagulation method)

A In almost any operative incision (breast neck abdominal wall etc) Do not coagulate near large vessels

B Coagulation of blood vessels during brain operations

IV Electrotomy (electrosurgical cutting)

A Coagulating electrotomy

1 Biopsy of accessible ulcerating neoplasms (oral cavity skin cervix bladder etc) using loop or blade electrotome

2 Excision of benign tumors (fibroma hyperplasia of gingiva etc) of mouth

3 Excision of malignant tumors of mouth including upper and lower jaw resections (bone severed with usual bone instruments with or without neck dissection)

4 Loop electrotome often used for removal of extensive cancer of antrum bladder etc preparatory to application of radium

5 Nasal polyps (snare technic)

6 Nephrotomy for stone Resection of kidney

B Fine electrotomy has no special advantage over scalpel for skin incisions and may delay healing It is useful for severing adherent loops of intestine and tumors and cysts adherent to intestine Using a loop electrode large and otherwise inoperable brain tumors may be excavated

CHAPTER 12

Special Considerations of Vascular Surgery Pertaining to the Treatment of Malignant Neoplasms

C Stuart Welch
and
Harry H Miller

SCOPE OF VASCULAR SURGERY IN CANCER

The special aspects of the surgery of blood vessels as they relate to the treatment of malignant neoplasms have to do with three major subjects the control of massive hemmorrhage the avoidance of serious accidents during operation and the special technics of operative surgery on blood vessels

Secondary ligations of major arteries are seldom required A thorough knowledge of the vascular anatomy of the body is essential to safe radical extirpative surgery Enthusiasm for extirpation may result in difficulties that are more serious in their consequence than is the cancer itself Uncontrolled hemorrhage may cause death at the operating table Severe ischemia of a vital organ or ischemic death of an extremity can be avoided by the knowledge of the functional significance of major arteries and veins Equally important is a good understanding of the physiology of circulation

The comparatively recent demonstration that segments of large vessels notably the aorta may be replaced satisfactorily by homologous vessel grafts suggests a wider application of this technic in extending the resectability of malignant neoplasms by providing for vascular reconstructions The limitations that the vascular system imposes on an operation for the adequate excision of cancer is sometimes the deciding factor against cure On the other hand a deficient circulation to vital organs or to needed body structures cannot be the end result of a good operation It may be that the use of graft replacements and vascular shunts can be more widely applied in overcoming some of these limitations

Much of this chapter is devoted to the anatomy of collateral circulation insofar as it affects blood supply after the ligation or excision of arteries and veins that are commonly involved in the extension of malignant tumors Some data on the use of vascular grafts are presented

CAUSES OF HEMORRHAGE IN PATIENTS WITH CANCER

Hemorrhage is to be expected in all large ulcerated advanced neoplasms especially in vascular regions when the wall of a medium sized artery is invaded by tumor Veins tend to become occluded by thrombosis from the surrounding inflammatory reaction more readily than do arteries and are less often the source of alarming bleeding Infection associated with malignant tumors is in large measure responsible for ulceration tissue destruction and vessel erosion This is particularly true for oropharyngeal growths With good local cleanliness hygiene and the present day specific antibiotic therapy this complicating feature of infected cancer can be minimized Hemorrhage also occurs as

the result of radiation necrosis of tumor tissue and is to be especially looked for when treating lesions of the tongue and floor of the mouth by irradiation Insidious but none the less serious bleeding may steadily take place from ulcerated growths occurring in the gastrointestinal or genitourinary tract The usual cause of hemorrhage after operation is the loosening of a thrombus from a medium sized vessel that was not adequately tied or upon relaxation of the spasm in a vessel that has retracted into the tissues A ligature may slip off It also may be brushed off by the surgeon during the course of the operation Needless to say, inadequate hemostasis during operation may be the cause of postoperative hemorrhage Bleeding may be on the basis of altered body physiology

THE TEMPORARY OR EMERGENCY CONTROL OF HEMORRHAGE

A number of simple procedures can reduce effectively the amount of blood loss if they are properly applied before supportive therapy or definitive surgical measures are administered

Blood vessels have natural hemostatic mechanisms Segmental arterial vasospasm occurring in a transected artery was recognized many years ago by John Hunter as of the greatest importance in arresting otherwise fatal hemorrhage The divided vessel is constricted and the cut ends retract by the contraction of its smooth muscle fibers Inversion of its outer layers then provides a mechanical barrier sufficient to impede the rapid arterial flow and thus allow an occluding clot to form within a few minutes Even in a large artery rapid exsanguination is often prevented by this natural mechanism The protective spasm however cannot be relied upon as a permanent measure because relaxation follows within a period of 24 hours A tangential perforation or an erosion of one wall of an artery presents a more dangerous source of bleeding

The initial maneuver in the emergency control of hemorrhage should provide a temporary check of rapid blood loss This can be accomplished often by pressure applied directly over the bleeding site If the vessel is exposed pressure of the fingers alone over the bleeding vessel can stem a furious hemorrhage A gauze sponge or pack applied with firm steady pressure over the bleeding site is ordinarily more effective since visibility is often poor at the site of hemorrhage If exposure is inadequate for the proper application of pressure the wound may be quickly enlarged by an extensive incision If bleeding is inaccessible as is the case at the base of the tongue a simple maneuver such as grasping and pulling the tongue forward may bring the point of hemorrhage within sight

The tourniquet has little usefulness in controlling hemorrhage and should be limited in its application to the more peripheral parts of the extremities where bleeding from a malignant tumor is of relatively minor importance

Control of the main arterial channel supplying a region of uncontrolled bleeding can be more rapidly applied in more diverse regions of the body by digital pressure than by tourniquet Almost all major arteries can be satisfactorily occluded by digital compression against the underlying skeletal system or other resistive structures In the case of the common carotid artery occlusion is accomplished by compressing it between the transverse process of the sixth cervical vertebra or Chassaignac s tubercle which lies at the level of the cricoid cartilage just anterior to the sternocleidomastoid muscle With the thumb pressing behind over the cervical spine the fingers are placed linearly along the line of the artery and one finger will strike the correct area where firm pressure can be exerted The inferior thyroid and vertebral arteries can also be compressed in this same general manner Certain tributaries of the carotid artery may be individually controlled The temporal artery is easily compressed against the zygoma just in front of the tragus of the ear The occipital artery can be shut off by digital pressure applied 3 cm lateral to the posterior occipital protuberance against the superior nuchal line along which the trapezius muscle inserts The external maxillary artery is easily compressed just in front of the masseter muscle where this vessel curves up to cross the mandible Smaller arterial divisions in the neck and lip are easily controlled by compressing the

buccal tissues grasped between the fingers It is not always possible satisfactorily to compress the subclavian artery digitally It is most superficial and exposed in its third part as it arches over the first rib Considerable pressure is necessary and is exerted by the thumb in an inward downward direction in that angle formed posteriorly by the clavicle and the sternocleidomastoid muscle More distally the brachial artery is easily compressed against the inner aspect of the humerus where the artery lies deep beneath the posterior margin of the belly of the biceps muscle Successful temporary control of the abdominal aorta in the thin individual may be possible by direct pressure applied through the abdominal wall In the obese or muscular individual such compression will not be effective and time need not be wasted in attempting it Pressure against the abdominal aorta should be directed somewhat above and to the left of the umbilicus so that the aorta is forced against the body of the third lumbar vertebra just above its bifurcation Although the iliac vessels are not accessible to direct compression the common femoral artery can be pressed against the superior ramus of the pubis This is done most easily by standing on the side of the patient s bleeding area and exerting perpendicular pressure with the finger tips against the pubis

Once vigorous hemorrhage is stopped by local measures more definitive procedures can be done in a deliberate fashion After allowing sufficient time for clotting pressure dressings may be carefully removed in the operating room and bleeding vessels exposed After using a hemostatic forceps to grasp the bleeding vessels they can be accurately ligated If bleeding vessels are not easily accessible in the wound or if the local tissue is friable because of the presence of necrotic tumor or gross infection the main artery supplying the region must be ligated

Major bleeding in the postoperative patient demands exploration of the wound In most instances the patient should be taken to the operating room and prepared as in an elective operation Transfusions of blood should be given concomitantly with preparation Except in the most dire necessity operation should not be done on the ward under conditions of poor lighting and inadequate preparation The older practice of evacuating large postoperative hematomas on the ward leads only to infection, and does not allow inspection for serious bleeding In the case of extensive wounds about the head and neck in which a large amount of blood has collected, opening and draining of the wound on the ward may be necessary and lifesaving in order to avoid respiratory obstruction Tracheotomy *may need to be done at the same time These* are exceptional cases and the general rule of taking care and time for transportation to the operating room does not apply in respiratory emergencies

All supportive therapy available should be used concurrently with efforts to check the bleeding

THE MANAGEMENT OF HEMORRHAGE AT OPERATION

In the course of extensive dissections about *major* vessels *alarming massive* hemorrhage may lead to disaster by injudicious instrumentation A common mistake often made when sudden or troublesome hemorrhage occurs is to neglect the urgent necessity for improving the surgical exposure It should also be kept in mind that the proximal control of major vessels is a sound principle when working in many regions Another basic principle to be remembered is that hand or finger compression rather than attempted clamping by instruments should always be the first choice in arresting serious massive bleeding Direct compression or proximal compression of arteries against a bony or resistant structure will often lessen bleeding so that the field may be dried sufficiently to apply a hemostat or ligature accurately When the latter is applied blindly in a pool of blood injury of important or even vital structures may produce great damage For example when the abdomen or thorax is opened the aorta can be readily compressed against the vertebral bodies The iliac arteries are accessible to compression against the bony pelvic brim *Hemorrhage from the hepatic* artery and other branches of the celiac axis can be checked by compression of these vessels between the fingers inserted through the foramen of Winslow In other regions the neck

the groin or the axillae any of the large vessels already exposed can be easily compressed Dry surgical gauze accurately applied directly to a rent in a major vessel and held for 5 to 10 minutes by the clock may also stop bleeding This will allow time for rapid blood replacement and permit deliberate exposure for definitive treatment of the vessel either by ligation or suture

The use of the suture ligature is one of the most effective and timesaving methods of hemostasis In soft friable vascular tissue that tears upon applying a hemostat a mattress suture that includes a good bit of tissue is at times indispensable The mattress suture is particularly valuable in resections of parenchymatous organs The mattress suture may be placed through and through and supported at either surface of the structure to be closed by intervening omentum subcutaneous fat fascia or other tissue Such tissue when included in the suture prevents the suture from cutting through a friable organ This type of suture placed in an interlocking fashion allows the resection of a large segment of the liver or kidney for example with adequate control of bleeding

The application of a hot (160 F) saline gauze pack to a briskly oozing raw surface is another effective method of hemostasis It must be left in place from 3 to 5 minutes or longer until clotting has occurred Heat accelerates coagulation so that bleeding rapidly subsides While the application of cold to bleeding areas may slow the rate of ooze by its vasoconstrictive effect the lowered temperature delays the coagulation process and is therefore less effective Muscle has been used for many years as a hemostatic agent particularly in neurosurgery Sutured in place as a tampon muscle liberates thromboplastin and hastens the natural coagulation process It has the disadvantage of becoming necrotic and is followed by some degree of fibrosis Its use has been largely replaced by absorbable hemostatic agents

Increased venous pressure owing to the obstruction of large veins draining the operative region is often a source of annoying bleeding at operation Ligation of veins therefore should be delayed in most cases until arterial inflow is controlled Of course early venous ligation may be desirable to prevent embolic tumor dissemination in some instances

In recent years there have been developed several hemostatic absorbable sponge materials that may safely be left in the body cavities The three materials most widely used are oxidized cellulose which is prepared through the oxidation of cotton by nitrogen dioxide the gelatin sponge which is made with a water insoluble gelatin base, and fibrin foam obtained from human plasma Fraction I When moderate quantities are used absorption is complete for each of these hemostatic agents within approximately six weeks These materials are useful for controlling moderate bleeding in situations in which hemostasis by ligature or sutures is difficult or technically impractical They cannot be expected to stop bleeding from large or medium sized arteries but will control a brisk ooze from a small artery and will stop venous or capillary bleeding They have been successfully used for patching tears in veins Fixation of the material with sutures is sometimes necessary A solution of thrombin is sometimes used in conjunction with hemostatic sponges particularly with fibrin foam

Electrocoagulation is useful in securing hemostasis in regions where ligature is awkward or where there is abundant circulation with diffuse bleeding The oral cavity is such a location The actual red hot cautery produces a more superficial coagulation by heat and is less satisfactory as an instrument of hemostasis

Styptics such as the silver nitrate stick and chromic acid bead are of limited but sometimes effective value in controlling oozing from skin lesions For large oozing surfaces the absorbable sponge preparations will serve the purpose better

Adrenalin when added to procaine in concentrations of about 1/100 000 for local anesthesia does much to eliminate the troublesome bleeding from the very vascular regions For local hemostasis 1 per cent procaine with adrenalin can sometimes be injected through a long fine needle into the vicinity of an actively bleeding vessel either at operation or when bleeding occurs in the

postoperative wound The locally increased tissue pressure from the bulk of fluid injected along with the vasoconstrictive action of the adrenalin decreases bleeding and may make it possible to locate and grasp a bleeding vessel with a hemostat

Ligation of Arteries and Veins

Ligation of a major artery is sometimes done as a preliminary measure before extensive dissection, in an emergency situation in the case of sudden hemorrhage or more commonly as a step in a planned procedure If done prophylactically, it may enable a more radical and adequate resection of tumor tissue or permit the performance of a procedure not possible without such control Viability of the part supplied by the vessel should be preserved in most instances for ligation of some major arteries may cause death or ischemic gangrene of important tissue At times the blood supply remaining after major artery ligation may be sufficient to maintain viability but inadequate to support normal function under conditions of stress The interruption of certain major peripheral arteries, particularly in the extremities frequently produces distressing functional impairment manifested by muscular weakness easy fatigability, susceptibility to cold atrophy, intermittent claudication and trophic changes with ulceration

Collateral Circulation

Collateral circulation is developed in channels that are not newly formed vessels but represent primarily small vessels that have undergone hypertrophy and enlargement in taking on a larger function The vascular pattern of collateral circulation is therefore already established before occlusion Certain regions have a better supply of collateral vessels and sustain arterial interruption more easily than others where the main artery can be considered critical The stimulus for collateral vascular development is apparently a mechanical one governed by the dynamics of blood flow

In almost all instances the volume of arterial collateral blood flow falls short of normal flow through the main vessel Even though the cross sectional area of the combined collateral channels carrying blood distally beyond an occlusion is equivalent to or greater than that of the original large vessel the quantity of blood that arterial collateral delivers is always less than that which a main artery supplied The quantity of flow through a vessel is proportional to the square of the area of cross section of the vessel That is to say, the total quantity of blood flowing during the same time through four small vessels of equal size will be only one fourth of that flowing in a single large vessel having the same cross sectional area as the four smaller ones

The length of small collateral channels is also of importance in that the resistance to flow within a vessel is proportional to its length In those instances in which collateral channels are short and return blood to main vessels just distal to the occlusion a pulsatile flow having a good pressure may be obtained whereas a much diminished flow results if the blood is delivered all the way to the capillary bed through small collateral vessels Pulsatile flow from the distal end of a divided artery (Henle Coenen sign) is found when there exist large collateral channels This finding may be interpreted to indicate an adequate collateral circulation Long collateral pathways on the other hand result in a dissipation of the force of the pulse These are important considerations in the resections and ligation of major vessels whenever good distal flow is needed As many as possible of the potential collateral vessels in the immediate region must be preserved for the best results

An important factor that may greatly influence the adequacy of collateral circulation is the pathologic state of the collateral channels and of the tissue to be supplied in any given individual The incidence of arteriosclerosis obliterans is highest in the age groups in which malignant tumors are most frequent

Radiation therapy produces an obliterative endarteritis with a resulting diminution of the blood supply to tissues that have been intensively irradiated In some cases massive gangrene of an entire irradiated region has followed arterial ligation This hazard must be kept in mind although it should not be

implied that previous irradiation always precludes arterial ligation

The time consumed in the process of occluding an artery is frequently crucial in determining whether or not a satisfactory circulatory adjustment will be attained During a slow occlusion as from a thrombus the collateral circulation will have the opportunity to develop over a period of days or weeks and development of an adequate collateral flow will have occurred by the time the artery is completely closed off An example in point of this sort of occlusion is found in the insidious thrombosis at the bifurcation of the aorta where a gradual occlusion seldom produces gangrene but where sudden occlusion often does This principle of the gradual occlusion of arteries as a preliminary step to their ligation and complete interruption has been known and used for a long time in clinical surgery Special clamps have been devised gradually to constrict major vessels Periarterial constriction by external irritants such as reactive cellophane rubber band elastic pressure and progressive suture closure of vessels are other technics used to attain the same end Some of these are described in the section on technics

The general status of the circulatory system and of the blood itself is another factor upon which effective collateral blood supply depends A good cardiac output with normal blood pressure is always desirable A state of shock or circulatory collapse will further deprive tissue lacking an adequate flow of blood through vasospasm of the small arteries and arterioles as well as from the hypotensive retardation of flow Severe anemia reduces the oxygen carrying capacity of the blood and whenever circulation is insufficient it adds to the severity of the ischemia

Peripheral vasodilation produced reflexly by external heating is the easiest and often most effective technic for improving the flow of blood in the smaller vessels Heat should not be applied to the ischemic part but rather to unaffected parts of the body The blocking of the sympathetic ganglia of the extremities with procaine may provide temporary vasodilatation and improvement in an ischemic member threatened with gangrene More permanent effect is obtained by surgical excision of the ganglia on the side involved General peripheral vasodilatation may be produced by numerous sympathetic blocking drugs These drugs have the disadvantage of producing a general fall in systemic blood pressure along with the widespread vasodilatation This fall in blood pressure can by itself produce an undesirable reduction in the volume of flow of blood peripherally to an ischemic part Generalized vasodilatation by drug therapy is therefore of questionable value in the treatment of local ischemia and may be harmful

Any ischemic part should be kept at rest in order to reduce its metabolic requirements For the same reason local warming which also raises the metabolic rate of the tissues should be strictly avoided In the case of extremities the affected part should be level with the recumbent body or slightly lower

Controversy exists over the question of the value of ligating the concomitant vein whenever an artery is accidentally or deliberately interrupted The theoretical basis for ligation of the companion vein rests on the idea that more blood will be retained in the ischemic part and more oxygen extracted in a given time Makins postulated from his observations on arterial injuries during the Boer War and World War I that vein ligation lowered the incidence of gangrene in arterial injuries Experimental support of the concept has been offered by Brooks *et al* Some of these fundamental experiments have been repeated recently and not confirmed Other studies using radioactive sodium clearance studies of muscle have shown no significant difference in the amount of blood in the tissue with and without concomitant vein ligation [16] Simeone *et al* present experimental data which indicate that ligation of the concomitant vein may be harmful Various clinical reports and advices continue to be contradictory The collected figures reported from series of arterial injuries in World War II also show that this procedure does not in any way increase the chances of survival of an ischemic extremity [19] The evidence of the value of ligation of a large vein companion to an interrupted artery is not well enough established to recommend it as an elective procedure Moreover

there is good evidence that it is harmful in *certain cases and may produce abnormal* edema and congestion

The surgeon must accept the fact that four important and basic considerations in *fluence the adequacy of collateral blood* supply when a major artery is interrupted at operation (1) The established anatomic vascular pattern of the region or organ in *volved is the first and unalterable factor* (2) The pathologic state of the individual's vascular system will determine the functional efficiency of his collateral vessels (3) The *time during which occlusion has occurred* i e, whether the interruption has been acute or gradual, may determine the end result (4) Last of all, the status of cardiac or *general cardiovascular function and* the quality of the circulating blood play some part in the picture

Interruption of Critical Arteries

Satisfactory data are available to allow of reasonable prediction of the results of arterial ligations or interruptions for all arteries of *the body and may serve as a guide for making* surgical decisions War data are more valuable than those obtained from civilian surgical cases since in the latter group arterial ligation is often performed for conditions in which an adequate collateral circulation has already developed viz, arteriovenous fistula *It is the* consequences of acute interruption of critical arteries in the virgin field that the surgeon must accept for making his plans in extirpative surgery

The indicated risk of serious ischemia following the ligation of major arteries as shown in Figure 12 1 presents estimations based upon collected statistical data reduced to approximate values They refer to acute interruption of the arteries in adults that result in functional insufficiency of the circulation with ischemia Loss of some part of an extremity or death of tissues necessary for life is the criterion on which these situations *are based* These figures do not refer to arterial interruptions in children or in individuals with predetermined adequate collateral circulation

Since arterial *injuries are not controlled* a coexisting destruction of collateral channels is commonly sustained which, coupled with shock and circulating collapse contributes to the high incidence of ischemia shown for each artery On the other hand the presence of degenerative vascular changes in patients undergoing cancer operations may be equivalent to factors associated with injury For practical purposes the figures for acute interruption by injury are the best to accept when deliberate sacrifice of one of these major vessels is at issue

Permanent occlusion by ligation of a major vessel for the emergency control of hemorrhage is required infrequently Whenever a choice can be made between arteries supplying a bleeding region the vessel which will control bleeding and do least harm is the first choice for ligation Sometimes there is little choice It is better however to stem bleeding by ligation of an artery selected to lessen and control local hemorrhage to some extent than to produce irretrievable damage by the ligation of a very critical artery The presence of infection and the extent of the neoplasm are some of the limiting factors in many cases *In Table 12 1 the vessels safest* to ligate for the control of bleeding in regions commonly involved by malignant neoplasms are listed Those designated as first choice *ligations are safer selections in that* permanent ischemia does not follow their interruption Second choice ligations carry a higher morbidity and often result in serious ischemia *Chances must* be taken in some cases since second choice ligation may be unavoidable when the first choice fails to control hemorrhage There are other factors also that allow of no choice such as the location or extension of the tumor

During the course of operative resection for cancer it is sometimes desirable to diminish the active circulation for the region by temporarily occluding a major artery [82] Prohibitive blood loss can be eliminated and the operative field kept relatively free of annoying bleeding In Table 12 2 are listed some of the permanent and temporary arterial ligations often employed in resections of malignant tumors for their value in aiding the technical performance and in lessening *the blood loss during operation*

Whenever temporary occlusion is practiced

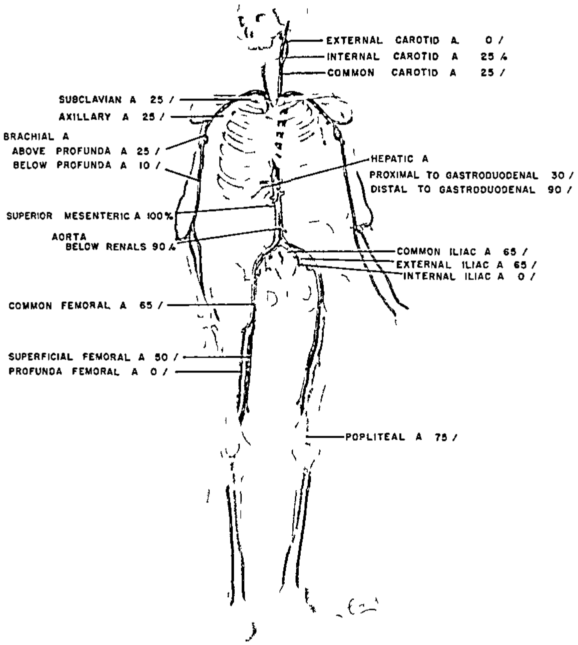


Fig 12 1 Percentage of serious ischemia after ligation of major arteries

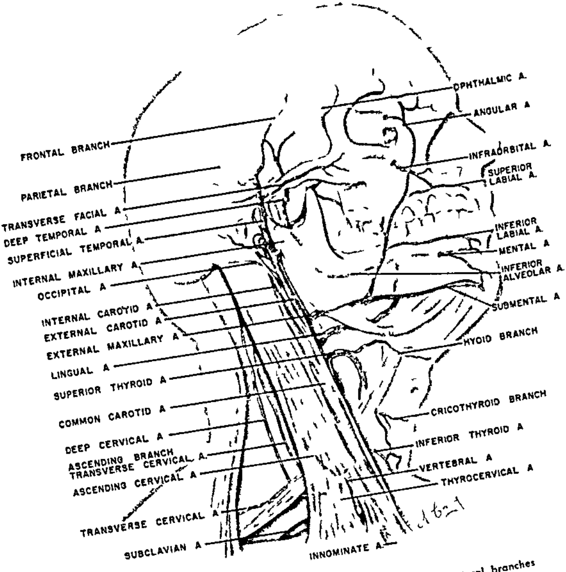


Fig 12 2 Arteries of head and neck with principal collateral branches

of the neck That it does not receive adequate collateral circulation from the external carotid has been shown by Sweet and Bennett In the case of ligation of one common or internal carotid artery the cerebral flow can be maintained by the carotid of the other side plus the basilar artery Blood from the contralateral carotid artery can traverse either or both of the anterior or posterior communicating channels Anatomic variation in the size or actual absence of either the anterior and posterior communicating arteries of the circle of Willis introduces one of the unpredictable elements in the results of carotid arterial ligation Sweet Sarnoff and Bakay have studied the efficiency of collateral circulation in the brain by direct manometric studies of the pressure in the carotid arteries distal to occlusion In certain individuals a comparatively small fall in pressure in the internal carotid artery was found to follow temporary occlusion of the common carotid of the same side In others pressure falls were great In one case bilateral common carotid occlusion did not result in a prohibitive reduction in internal carotid artery occlusion A fall in pressure to 30 per cent of the original level is considered by these investigators to be an indication that carotid artery ligation is unsafe It may be that direct pressure studies of the carotid artery after temporary occlusion during operations on the neck for cancer may allow of a safe decision for or against excision of a segment of this artery

Fortunately the need for common carotid ligation occurs infrequently Hemorrhage about the head neck and face is better controlled by external carotid ligation However in those cases in which access to the external carotid is impossible because of the presence of a tumor or infection in the region the common carotid must be ligated lower in the neck In certain cases with involvement of the common carotid by either metastatic tumor or an extensive malignant carotid body tumor ligation and excision of the common carotid artery may be indicated Pemberton and Livermore believe that anticoagulant therapy offers hope of reducing the mortality following ligation of the carotid vessels

Anatomy The course of the common carotid artery is indicated by a line drawn from the sternoclavicular articulation to a point midway between the angle of the jaw and the mastoid process On the right side the artery originates as a branch of the innominate artery where it divides behind the upper border of the right sternoclavicular articulation On the left the common carotid arises from the arch of the aorta just below the junction of the cartilage of the first rib and the sternum The arteries in their oblique course up the neck lie on either side of the esophagus and trachea under cover of the inner border of the sternocleidomastoid muscle The artery is contained in a sheath derived from the deep cervical fascia which also encloses the internal jugular vein as it lies lateral to the artery The vagus nerve lies posteriorly between the artery and vein The descending hypoglossal nerve lies on the carotid sheath anterior to the artery Frequent abnormalities of size length and number of branches are found in the individual anatomy of the carotid artery The level of bifurcation is variable It may occur as high as the hyoid bone and as low as the cricoid cartilage Its normal location is at the upper border of the thyroid cartilage and in about one half the cases the bifurcation is at this point

Surgical Approach Section or excision of the artery is safer than ligation in continuity because of the lessened danger of cerebral embolism [78] Ligation of the common carotid may be done either above the level of the omohyoid muscle or below it The omohyoid muscle crosses the artery at the level of the cricoid cartilage It is preferable to ligate the common carotid artery above the muscle where it lies more superficial and is more accessible where covered with fewer structures When local conditions in the neck preclude a satisfactory operative field above ligation is done just below the omohyoid muscle The patient should be placed on his back with his shoulders elevated and the neck extended The face should be turned slightly to the opposite side

In approaching the common carotid artery in the superior carotid triangle a 6 cm incision is made in line with the vessel along the anterior border of the sternocleidomastoid muscle The incision should be centered at the level of the cricoid cartilage Transverse inci

sions produce better cosmetic results when they can be used [37] The skin superficial fascia platysma muscle and superficial layer of the deep fascia are divided in that order The sternocleidomastoid muscle is retracted laterally and the omohyoid muscle downward The medial wall of the sheath is opened to expose the artery

If the artery is to be ligated below the omohyoid an incision 6 to 7 cm in length is made along the anterior border of the sternocleidomastoid muscle from the level of the cricoid cartilage almost down to the sternal notch The superficial structures including the skin superficial fascia and platysma muscle are likewise divided in that order The sternocleidomastoid is exposed and drawn outward and the sternohyoid and sternothyroid muscles covering the thyroid are drawn inward The internal jugular vein is retracted laterally after incision of the carotid sheath Care must be exercised in order to avoid injury to the vagus nerve which lies lateral and posterior to the artery

In the operation of ligation of the common carotid artery preliminary gradual occlusion may be undertaken to lessen the likelihood of cerebral difficulties In 1901 Crile described a *spring clamp that could be applied to the* artery and slowly tightened to bring about a gradual occlusion Selverstone has devised an ingenious clamp that may be placed on the common carotid artery and gradually tightened over the course of days Gradual occlusion is useful in the treatment of intracranial aneurysm but probably has little place in surgery of the neck for cancer Whenever ligation of the common carotid is contemplated during the excision of a neoplasm of the neck temporary occlusion of the artery for 30 minutes should precede its sacrifice Local anesthesia should be employed at this time in order to make adequate observations of the cerebral effects

THE INTERNAL CAROTID ARTERY

The indications for ligation of the internal carotid artery alone in operations for malignant neoplasms are rare It may be injured in a dissection of the region hence its inclusion in this book Since there is no significant collateral flow retrograde from the external carotid artery the ligation of the internal carotid artery produces an effect essentially the same as ligation of the common carotid artery [91]

Surgical Approach The surgical approach to the lowest segment of the internal carotid artery is the same as for exposure of the common carotid artery in the upper triangle of the neck At the bifurcation of the common carotid artery the common facial vein is divided as it enters the internal jugular vein The internal carotid artery branches somewhat anterior and lateral to the external carotid artery If a larger exposure is necessary it can be attained by freeing the parotid gland and retracting it upward taking care to preserve the facial nerve The posterior belly of the digastric muscle and the stylohoid muscles may be divided and the mandible may be divided after the maxillary angle is exposed by incision of the masseter muscle This exposes the upper segment of the mandibular ligament which may be divided and the styloid process removed in order to allow the internal carotid to be visualized as it enters the base of the skull (For further discussion of methods of lessening the hazards of carotid artery resection see Volume III Chapter 42)

THE EXTERNAL CAROTID ARTERY

Ligation of the external carotid artery is most valuable in control of hemorrhage from malignant tumors about the face tongue jaw nose nasopharynx and mouth Ligation of this artery is often used as a preliminary procedure or as an initial step in operations involving extensive resections of the mandible tongue or maxilla Its ligation is not accompanied by the hazards of common or internal carotid artery ligation since it does not contribute significantly to cerebral circulation Only in rare cases that have been intensively irradiated or in which important collaterals have been divided at operation may massive gangrene follow external carotid artery ligation Ordinarily unilateral ligation will be sufficient for the control of hemorrhage but the opposite external carotid artery may be safely ligated also if it seems necessary The harmlessness of external carotid artery ligation is an attribute of the rich collateral arterial channels that feed it

Anatomy The external carotid artery has a slightly curved course upward from its origin at the site of bifurcation of the common carotid (Figure 12 2) In its first part the superior thyroid branch leaves it medialward and hooks downward Two to 3 cm above the superior thyroid artery the lingual artery branches from it in the same direction which serves to identify the carotid artery in this location Anterior to the external carotid artery at the level of the lingual artery the hypoglossal nerve traverses it At a slightly superior level it is crossed by the stylohyoid muscle and the posterior belly of the digastric muscle The artery then passes backward behind the neck of the mandible into the substance of the parotid gland where it terminates as it divides into the superficial temporal and internal maxillary arteries

Surgical Approach The site of election for ligation of the external carotid artery is below the digastric muscle between the superior thyroid and lingual arteries The patient is positioned as he is for ligation of the common carotid artery The skin incision is made along the anterior margin of the sternocleidomastoid muscle just below the mandibular angle and extends downward for about 6 cm The platysma muscle and the superficial cervical fascia along the edge of the sternocleidomastoid muscle are divided The common facial vein is divided where it crosses the bifurcation of the carotid The sternocleidomastoid muscle is retracted laterally exposing the carotid sheath which is in turn incised The descending branch of the hypoglossal nerve is drawn medially and the internal jugular vein laterally The external carotid artery may then be identified dissected free divided and ligated The abundant collateral circulation may be further diminished by ligation of the superior thyroid lingual and other accessible branches The surgical approach to the external carotid artery is shown in Figure 12 3

LINGUAL ARTERY

Ligation of the lingual branch of the external carotid artery is sometimes performed to decrease bleeding in the operation of glossectomy and may be necessary for the control of hemorrhage in advanced cases of cancer of the tongue Adequate collateral blood flow for viability is obtained via the contralateral lingual artery and the pharyngeal branches of the external carotid to the base of the tongue Bilateral lingual artery ligation may cause gangrene of the tip of the tongue

Anatomy The lingual artery usually is the third branch of the external carotid artery and arises near the greater cornu of the hyoid bone As it leaves the external carotid it forms an upward loop rising above the cornu of the hyoid bone It then passes beneath the stylohyoid and digastric muscles and runs along the upper border of the hyoid bone beneath the hyoglossus muscle before it ascends directly into the tongue

Surgical Approach The lingual artery is exposed deep in the submaxillary triangle (Figure 12 3) A transverse incision through skin and platysma is made beginning just anterior to the tip of the mastoid process and is carried down over the hyoid bone to the submental region The submaxillary salivary gland usually protrudes through the incision and is retracted upward A triangular area bounded inferiorly and posteriorly by the digastric muscle and anteriorly by the mylohyoid muscle is exposed The floor is formed by the hyoglossus muscle The hypoglossal nerve and lingual artery run medialward and diagonally upward across the hyoglossus muscle The lingual artery is exposed by pulling the hypoglossal nerve upward and by dividing the hyoglossus muscle fibers below it Upon separating these muscle fibers the lingual artery is exposed where it may be ligated and divided The artery may also be ligated at its point of origin by an exposure similar to that for the external carotid artery

SUBCLAVIAN AXILLARY AND BRACHIAL ARTERIES

An occasion for resection of the subclavian axillary or brachial artery is rare on account of its involvement by metastatic or primary cancer Usually the cancer is widespread when these vessels are involved Hemorrhage in the arm from a neoplasm distal to the subclavian artery that required ligation would be unusual and might best be treated by amputation In the interscapulothoracic am

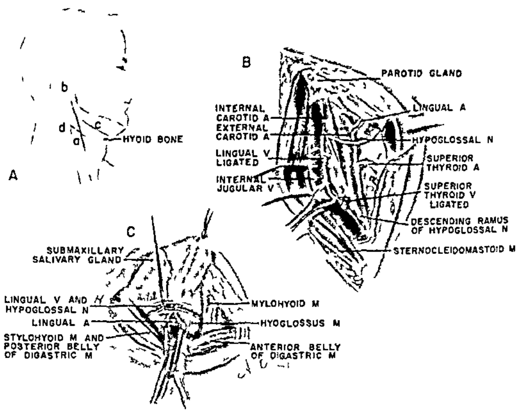


Fig 12 3 Surgical approaches to external carotid and lingual arteries *A* Incisions *a* A vertical incision is made along anterior border of sternocleidomastoid muscle and centered at level of hyoid bone for exposure of carotid bifurcation *b* Showing extension of incision *a* upward by dividing sternocleidomastoid muscle for further upward exposure *c* Transverse incision just above the hyoid bone may be used for approach to lingual artery *d* Showing a transverse incision through skin and platysmus muscle Carotid bifurcation may be exposed after sternocleidomastoid muscle is retracted This incision produces a minimal scar

B Approach for ligation of the external carotid artery Sternocleidomastoid muscle and internal jugular vein are retracted laterally to expose carotid vessels after dividing branches of the internal jugular vein

C Approach for ligation of the lingual artery The lower pole of the submaxillary salivary gland is retracted upward and fibers of the hyoglossus muscles are separated to expose the lingual artery which courses transversely deep to this muscle

putation the subclavian vessels are exposed and controlled early in the operation

In the infant or child with a congenital cardiac defect transection of the subclavian artery has been shown to be followed by no serious impairment of the circulation to the arm [7] In the older individual in whom collateral vessels are damaged or diseased some degree of tissue loss may result in from 25 to 45 per cent of individuals in whom the subclavian artery is interrupted Plans for the use of an arterial graft should be made whenever resection of the subclavian is anticipated The risk attending axillary or brachial artery occlusion above the profunda branch is about the same as for the subclavian artery insofar as the viability of the arm is concerned Below the branching of the pro funda the brachial artery may be ligated with impunity in elective cases when there is no extensive bone injury Warren is of the opinion that ligation of the axillary artery or brachial artery either above or below the profunda in a young individual with intact collaterals is completely safe Ligation of either ulnar or radial arteries is safe

Anatomy The subclavian artery is ana tomically divided into three parts (Figure 12 4) The first part extends from its origin from the innominate artery on the right side On the left side the subclavian artery arises from the arch of the aorta The second part lies posterior to the scalenus anticus muscle *and the third part lies between the lateral edge* of this muscle and the outer border of the first rib There it ends to continue as the first part of the axillary artery The axillary artery extends to the outer border of the teres major muscle where it continues as the brachial artery In the upper third of the arm the chief branch of the brachial artery is the profunda brachii and this branch is very important to the integrity of the forearm and hand if the brachial artery is ligated below it

The subclavian artery is usually ligated by election in its third part When ligated at this point the main collateral channels con sist of the anastomoses of the branches of the internal mammary intercostal transverse scapular and transverse cervical arteries with the more distant branches of the thoraco acromial lateral thoracic and subscapular arteries Ligation of the axillary in its first part above the thoracoacromial trunk pro duces the same effect as division of the third part of the subclavian artery When the axillary artery is ligated at its lower end (third part) the main collateral channels are similar to those for obstruction to the upper part of the brachial artery These collateral routes are made up of anastomoses between the anterior and posterior humeral circumflex arteries and the branches of the subscapular and thoracoacromial arteries as they join the profunda brachial artery At the elbow the profunda brachii and the ulnar collateral arteries anastomose with the ulnar and radial recurrent arteries to provide a rich collateral network The names subclavian axillary and brachial are only terms used for the convenience of teaching and learning classic anatomy and have no functional significance The main artery to the arm with its branches is the functional unit Branches vary in each individual and adequate exposure is essential for identification of collaterals

Surgical Approach The classic approach to ligation of the third part of the subclavian artery is made through a transverse incision parallel to the clavicle with the dissection carried down posteriorly between the clavicle and chest wall This gives however an un satisfactory and limited exposure of the vessel The exposure obtained by division or resec *tion of part of the clavicle is much safer and* may be quickly performed in an emergency [22] (Figure 12 5) The incision may be extended downward widely to expose the axillary vessels or may be carried upward to expose the vessels of the neck This is best done with the arm outstretched and *with a sandbag beneath the shoulders* The transverse incision along the clavicle exposes the periosteum which is elevated and the mid segment of the clavicle is removed after dividing it with a Gigli saw The subclavian vessels come into view when the periosteum and superficial fascial layers are incised For greater exposure the incision may be extended along the lateral border of the sternocleidomastoid muscle as shown in Figure 12 5 [35] The edge of this latter muscle may be further divided medialward at its

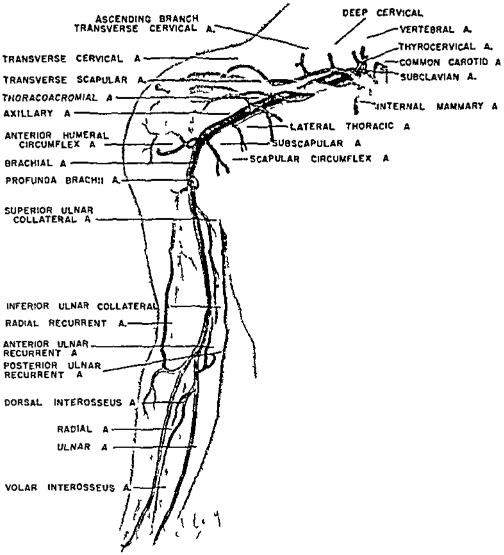


Fig 12-4 Arteries of the upper extremity and shoulder girdle with principal collateral branches

clavicular attachment Complete exposure of the vessels from the root of the neck through the axilla may be obtained by carrying the incision down from the clavicle over the shoulder anteriorly In closing the wound the resected section of clavicle need not be replaced since no disability follows its loss The axillary artery may be exposed alone by an oblique transverse incision continued from the lower part of the incision shown in Figure 12 5 The pectoral muscles are divided as shown The third part of the axillary artery can be exposed for a limited extent by an incision overlying it in the outer part of the axilla while the arm is held out stretched and forearm supinated In the upper arm the brachial artery is found beneath the medial edge of the biceps muscle anterior to the triceps brachii It can be exposed by an incision paralleling the artery down the arm It is closely associated with its venae comitantes and is crossed by the median nerve superficially near its mid portion The collateral circulation in the arm is better than in the leg and ligations of major vessels in the upper extremity are safer than in the lower

THE ABDOMINAL AORTA

Ligation and resection of the abdominal aorta below the renal vessels has been performed almost entirely for the treatment of aneurysm or thrombosis Although the collateral circulation should be more highly developed in these lesions only approximately 30 per cent of these patients have survived ligation of the aorta Gangrene or erosion of the vessel with exsanguinating hemorrhage is common following aortic ligations Severe and immediate arterial insufficiency to the extent of causing death of both extremities and paraplegia often results Lesser sequelae that have been reported are paralysis loss of sensation due to spinal cord damage and ischemic ulceration over the sacral region As collateral circulation gradually develops a regression of these defects and a progressive return of a fair degree of function may be expected A few instances in which aortic ligation has been done for tumor have been reported An aortic segment into which a neuroblastoma had extended was successfully excised by Ladd in the case of a child who has not presented subsequent difficulties and is without evidence of recurrence The outlook for successful aortic ligation is more hopeful either in the young individual free of arteriosclerosis or in one who has already adapted to a partial occlusion of the vessel On the whole however aortic ligation or excision with ligation should be considered impractical in the surgery of cancer The end results are too devastating to make it worthwhile

There are three main routes of collateral flow when the abdominal aorta is interrupted below the renal arteries and care should be taken to save these vessels at operation Blood flows distally through the anastomosis of the superior hemorrhoidal branch of the inferior mesenteric artery with the inferior hemorrhoidal branches of the internal iliac arteries The superior epigastric vessels join the deep inferior epigastric arteries on either side these latter are branches of the external iliac artery The two lower lumbar arteries join with the deep iliac circumflex and iliolumbar arteries to form a third group of collateral pathways These are rather feeble collateral routes for the needs of the extremities The blood supply to the spinal cord via the lumbar arteries is always jeopardized by excision of a segment of the aorta and this is a major factor that adds to the difficulties of its resection for neoplasm

The highly questionable procedure of aortic ligation is definitely restricted to levels below the renal arteries and the superior mesenteric artery If surgical procedures are anticipated for the aorta more proximally replacement or repair must be planned There is a limitation of the time allowable for arterial occlusion in performing surgical procedures on the aorta The clever technic developed by Hufnagel whereby an aortic graft is sutured while a temporary plastic prosthesis within the graft transports the blood offers one the means of replacing a section of aorta How much segmental replacement of the aorta can accomplish remains for the future to disclose The outlook for the procedure carried out for neoplastic disease is doubtful for even though the technic may be worked out satisfactorily very few neoplasms will

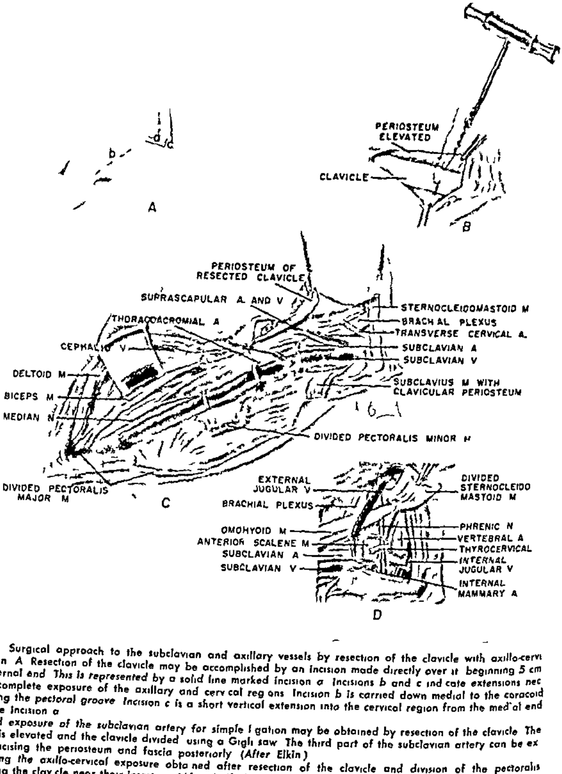


Fig 12 5 Surgical approach to the subclavian and axillary vessels by resection of the clavicle with axillo-cervical extension A Resection of the clavicle may be accomplished by an incision made directly over it beginning 5 cm from the sternal end *This is represented* by a solid line marked incision *a* Incisions *b* and *c* indicate extensions necessary for complete exposure of the axillary and cervical regions Incision *b* is carried down medial to the coracoid process along the *pectoral groove* Incision *c* is a short vertical extension into the cervical region from the medial end of transverse incision *a*

B Limited *exposure of the subclavian artery for simple l*igation may be obtained by resection of the clavicle The periosteum is elevated and the clavicle divided using a Gigli saw The third part of the subclavian artery can be exposed by incising the periosteum and fascia posteriorly *(After* Elkin*)*

C Showing the axillo-cervical exposure obtained after resection of the clavicle and division of the pectoralis muscles along the clavicle near their insertion *(After* A K Henry*)*

D The anatomic *relations of the first* and second parts of the subclavian artery are shown This exposure may be obtained by medial extension of the incision and division of the clavicular head of the sternocleidomastoid muscle

be encountered in which the procedure is justified

The operative approach to the distal part of the abdominal aorta is through a low mid line abdominal incision which may be extended upward to the left or right of the umbilicus Access to the aorta is gained transperitoneally by making a vertical incision over it just to the left of the mid line There has been much discussion and investigation of methods of aortic ligation When ligation is performed it is safer to divide it also This avoids having the full force of the pulse wave strike a relatively fixed point as is the case in the undivided vessel At the ligation site, the elasticity of the vessel wall permitting longitudinal movement of the divided end absorbs a sizable part of the shock of the pulse Ligation with broad bands of catgut tape fascia elastic rubber and other substances has been advised Successful ligation has been accomplished using No 2 chromic catgut ligatures The technic of suture closure of the divided vessel end with a double crossed continuous type of stitch has been demonstrated to be effective by Swan and Harper in experimental studies

THE MESENTERIC ARTERIES

The intestinal tract from the ligament of Treitz down to the mid portion of the transverse colon comprises the midgut and is supplied essentially by a single vascular unit made up of the superior mesenteric artery and vein These vessels pass beneath the head and body of the pancreas and the transverse mesocolon Here they are often invaded by tumor that has extended from nearby viscera When invasion of the tissue by tumor about the superior mesenteric vessels is present a contraindication to radical resection of tumors is usually considered to exist This is especially pertinent in the case of carcinoma of the head of the pancreas Sudden occlusion of either of these vessels if allowed to persist is fatal because of insufficient collateral vessels to take over their function Arterial flow from the inferior mesenteric to the superior mesenteric artery by way of the left colic and midcolic arteries can take place but is inadequate There are venous anastomoses between the portal and systemic systems but these are not ordinarily sufficiently developed to permit acute portal obstruction If occlusion of the superior mesenteric vein has occurred as the result of gradual obstruction by tumor the collateral routes may be developed enough to allow safe resection of the superior mesenteric vein or portal vein These cases are rare

More attention should be given to the problem of rerouting the flow of blood from the superior mesenteric vessels and also to the replacement of these vessels Anastomosis of the superior mesenteric artery and vein to corresponding renal vessels after nephrectomy could be done It may be possible in certain instances to join one of the larger small intestinal mesenteric vessels with the inferior mesenteric artery

The vascular pattern in the mesentery of the small bowel provides within it, collateral routes that safely permit resection of part of the mesentery with preservation of the corresponding segment of intestine The mesenteric intestinal circulation of a number of species, including man has been studied with respect to its revascularization potential [63] In man there are 12 to 16 intestinal arteries to the small intestine which join laterally forming a series of arcades, the arcuate vessels These arcades become more complicated in the more distal loops of small intestine The arcuate arteries give off short vessels vasa recta which pass directly to the bowel without intercommunication These arteries on entering the intestinal wall become the mural trunks which do have sizable anastomotic communications that have an oblique course within the bowel wall The jejunum and upper ileum are especially richly supplied with the mural vessels In the lower ileum this intramural anastomosis tends to be plexiform an arrangement which provides less efficient anastomoses Two possible sources of collateral circulation to a segment of bowel the mesentery of which proximal y is damaged are therefore through the arcuate system and through the mural vessels within the bowel wall itself Of the two the arcuate system is more effective so that in dogs it is possible to revascularize as much as 25 cm segments through these channels The maximum that can be revascularized with both the

arcuate vessels and vasa recta ligated has been shown experimentally to be between 5 and 6 cm, and up to as much as 15 cm has been possible in some animals [63] These results have been obtained in the dog whose intramural anastomoses are inferior to those of man An important related consideration is the pronounced interference with intramural arterial anastomoses brought about by intestinal distention

The utilization of the capacity of the arcuate system of vessels to supply a long segment of intestine was first suggested by Roux and more recently applied by Yudin A jejunal segment was brought up to replace the thoracic esophagus Gangrene of such jejunal loops has frequently followed their displacement Longmire believes that the initial division of two primary mesenteric arteries can be done with impunity but that before dividing the third and fourth sets the vessels should be temporarily occluded for 5 to 10 minutes and the circulatory function observed The presence of a palpable pulse, good color and normal activity is a good criterion of adequate circulation An anastomosis between the mesenteric vessels and regional vessels of comparable size has been suggested Longmire successfully did this in a young boy whose resected esophagus he replaced by jejunum after anastomosing the intestinal vessels to the internal mammary vessels Stage division of the mesenteric vessels permitting collateral development is another technic and this has been demonstrated to be effective in lessening the chance of gangrene in experimental studies and in clinical cases

The experimental work of Nelson and Kremen suggests that if there is an anticoagulant effect from the administration of an anticoagulant such as heparin at the time of superior mesenteric vein occlusion this procedure may be sustained Apparently by preventing intravascular thrombosis in the retarded circulatory system of the intestine collateral channels are able to assume adequate function This could not be expected however once occlusion had been established for some time and thrombosis had been allowed to occur In the case of superior mesenteric artery occlusion heparinization was not as effective although through its use the time of its occlusion could be safely extended from a 2 hour limit to 4 or 5 hours The employment of an antibacterial preparation to reduce the bacterial flora of the intestine also increased the number of survivals after temporary arterial occlusion

In colonic resections the arterial pattern has long been recognized as a deciding factor in selecting the type of surgical procedure Resection of the ascending and transverse colon or segmental resections of the left colon present few vascular problems In extensive resections of the left colon that are designed to remove a wide area of lymphatic bearing mesentery it appears desirable to resect the inferior mesenteric artery along with its major branches In doing this a long segment of colon may be left that is dependent solely upon the middle colic artery by way of the marginal artery which anastomoses with the terminal branches of the left colic arteries The entire rectum above the levatores ani muscles and the colon as far as the mid descending colon may be excised together with the inferior mesenteric artery and its mesentery providing the marginal vessels of the descending colon are preserved Thus in anterior resections of the rectum and in combined abdominoperineal resections of the rectum the region about the inferior mesenteric and up along the aorta may be included in the dissection Operations for rectosigmoid and sigmoid lesions are probably inadequate unless the inferior mesenteric vessels are sacrificed and a thorough dissection is performed The marginal artery of Drummond forms a series of anastomotic loops from the ileocolic artery to the sigmoidea ima It is this artery that supplies the link between the middle and left colic arteries This important communication is reported by Grant to be absent in only 5 per cent of individuals Sudeck s or Hartman s critical point has received much attention in discussions of rectal and sigmoid resections in older literature This point on the inferior mesenteric artery just above the origin of the last sigmoid artery was described as being the safest site for ligation in mobilizing the colon at this level Ligation below this point was believed to interrupt the anastomosis between the last sigmoid artery above and the superior hemorrhoidal artery

below and so as to compromise the circulation of either the distal sigmoid or proximal rectum It is apparent that with the considerable variation in vascular patterns for the intestine the significance of Sudeck s point will differ with the individual s vascular arrangement and with the type of operation that is performed In abdominoperineal resection ligation of the inferior mesenteric arterial tree at the classic site i e the sacral promontory is well above the critical point In end to end rectosigmoid anastomosis however the point acquires importance The pattern of the sigmoid arteries shows considerable variation Usually there are 1 to 4 arteries arising from the inferior mesenteric artery or left colic artery but as many as 7 have been described Some investigators have regarded the sigmoidea ima artery as a branch of the inferior mesenteric artery below and distinct from the lowest sigmoid artery By anastomoses with the lowest sigmoid artery the sigmoidea ima completes the vascular arcade of the marginal artery and is found to be present in 81 per cent of cases While its branches supply the rectosigmoid its importance lies in the existence of significant anastomoses between it and the superior hemorrhoidal artery found in half of the cases examined In the half of cases showing this arrangement ligation of the inferior mesenteric artery below Sudeck s point should not deprive the colon of its blood supply whereas in the other half without such anastomoses vascular impairment should be expected The question of a critical point for ligation of the inferior mesenteric arterial tree is somewhat artificial and classic points should be disregarded in favor of performing an adequate radical excision In a limited series of cases in which an extensive sigmoid and distal left colon resection has been performed removing all the mesentery included with the inferior mesenteric artery the marginal artery has been found adequate in performing colonic rectal anastomosis If doubt exists as to the adequacy of the circulation the artery in question can be temporarily occluded and its effects observed In surgery of the colon alteration of the operative procedure to suit the blood supply is much more readily done than elsewhere The final test after any ligation of arteries to the colon is its functional blood supply which can be readily observed either by visualizing the pulsations in small vessels or by observing its capacity for arterial bleeding

THE HEPATIC ARTERY

Ligation of any part of the hepatic artery is generally considered to be hazardous and may result in fatal hepatic dysfunction The occurrence of an hepatic death within 3 to 4 days after the operation of cholecystectomy has been ascribed to occlusion of one of the main branches of the hepatic artery usually the right branch Cases of survival following known hepatic artery occlusion have been reported In these instances the presence of large collateral arteries joining the hepatic artery distal to the site of ligation is presumed to be the fortunate case The gastroduodenal and right gastric arteries are the principal vessels that form such anastomoses The location of the hepatic artery makes it vulnerable in extensive operations for the excision of malignant tumors in the stomach pancreas and biliary tract Even though it is not involved in the tumor itself the hepatic artery may be inadvertently injured at operation particularly during resection of the head of the pancreas

The normal hepatic artery originates from the celiac axis and gives rise to the large gastroduodenal artery and the right gastric artery It then divides into two main hepatic branches These divide subcapsularly into approximately 20 to 30 terminal hepatic branches that enter the liver substance The liver seems to be supplied in a regional fashion by these branches The extent of intrahepatic arterial anastomosis is not known In the human liver there are subcapsular anastomoses between the phrenic arteries by way of vessels in the coronary and triangular ligaments and the bare areas of the liver While there are also rich extrahepatic communications between twigs of the terminations of the hepatic branches in the fossa for the umbilical vein about the caudate lobe it is doubtful because of their size that these can carry on the circulation when a large branch such as the right hepatic is ligated In almost half of 200 bodies carefully examined [57]

some sort of aberrant hepatic artery was found to be present In 11 5 per cent of in stances the left hepatic artery arose from the left gastric artery and in 12 5 per cent the right hepatic originated from the superior mesenteric artery In 5 cases (2 5 per cent) the entire hepatic trunk was derived entirely from the superior mesenteric artery In one case out of approximately 500 the hepatic artery was found to arise from the left gastric artery alone Awareness of these aberrant vessels is of special importance in carrying out the division of the left gastric artery during radical resection of the stomach for cancer The hepatic artery should be ex amined and palpated for its pulsation In the operation of pancreaticoduodenectomy the possibility that the superior mesenteric artery gives rise to the hepatic artery demands consideration

Experimentally, numerous attempts have been made to obviate the fatal results of hepatic artery ligation Procedures to increase the oxygen saturation of portal vein blood have been conceived and applied successfully to animals This was first done by Narath with uncertain results and recently carried out effectively by Schilling *et al* These in vestigators created an end to side arterio venous fistula between the divided hepatic artery and portal veins and obtained survival of all animals It is suggested by this work that in case of hepatic artery injury when no other alternative is available some sort of portal arteriovenous fistula—such as be tween the splenic artery and vein—could be tried However it is likely that in this event the portal vein itself might also be destroyed and this type of maneuver would not then be feasible in such an injury Reconstruction of the hepatic artery is the better choice Welch and Callow report the successful suture of an hepatic artery divided during a pancreatico duodenectomy for carcinoma Here approxi mation of the vessel ends was possible If approximation of the vessel ends is not pos sible either an arterial homograft or an autog enous vein or artery graft taken from the brachial artery or a forearm vein could be implanted It is important to bear in mind that arteries as small as the hepatic artery can be successfully anastomosed

It is believed by some investigators that a function of the arterial blood from the normal hepatic artery is to maintain oxygen at a level incompatible with the proliferation of anaerobes that are constantly present in hepatic tissue [51] The studies of Tanturi *et al* indicate that in the dog lecithinase the alpha toxin of *Clostridium perfringens* type A is the most important factor in causing death from hepatic artery ligation Dogs whose hepatic arteries were ligated sur vived when given parenteral Aureomycin for 5 days and these animals showed no necrosis of the liver at autopsy [27] Under antibiotic therapy changes in liver function owing to lack of arterial supply were observed to be mild and it was concluded that the dep rivation of arterial blood per se is not the cause of death in hepatic artery occlusion

Recently there has been support of this concept in human clinical cases Ligation of the main hepatic artery along with the splenic artery has been successfully accomplished in cases of portal hypertension due to cirrhosis of the liver [76] The rationale of the pro- cedure is that removal of the high pressure arterial blood from the liver s circulation permits more ready passage of the venous blood of the portal system through the liver Streptomycin and penicillin were given these patients both before and after operation The main hepatic artery was ligated distal to the departure of the gastroduodenal artery which would seem to eliminate any collaterals of significant size The experimental work of Grindlay, Mann and Bollman did not show that penicillin protected the liver of dogs from all the effects of deprivation of arterial blood The recovery of animals was related to the development of adequate collateral vessels presumably in the diaphragmatic ligaments and along the surfaces of the bile ducts and vena cava and possibly through adhesions Necrosis of liver substance was seen in regions in which arterial supply was entirely absent While it is not known whether these observations can be applied clinically to all human cases they do strongly emphasize the necessity for massive antibiotic therapy when the hepatic arterial supply is threatened

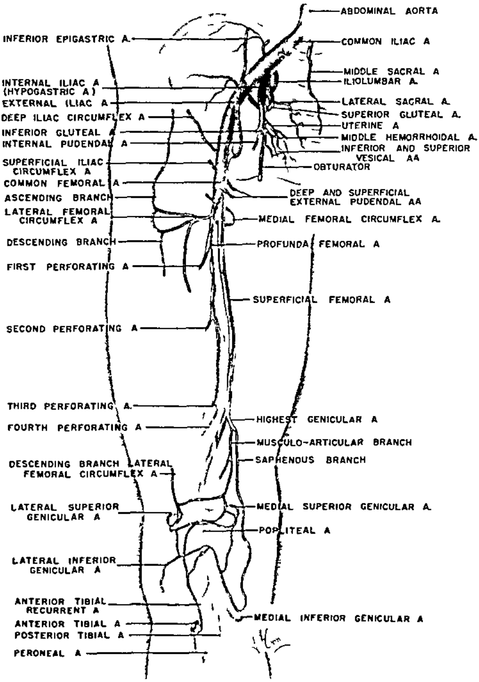


Fig 12-6 Arteries of pelvis and lower extremity with main collateral branches

THE COMMON AND EXTERNAL ILIAC ARTERIES

Sudden permanent occlusion of the common or external iliac artery puts the extremity in jeopardy. The incidence of gangrene is at least 65 per cent following ligation of either of these vessels. On the other hand, ligation of the internal iliac artery (hypogastric) is without serious consequence. As the iliac vessels pass along the brim of the pelvis, they are in a vulnerable area for involvement by metastatic cancer arising from the pelvic organs. If the artery is involved, it is likely that the adjacent nerves and bony structures are also, so resection is usually precluded for reasons other than the vascular involvement. Should resection of a tumor together with either the common or external iliac artery, be feasible, replacement of the resected segment with a vessel graft is desirable rather than attempted simple ligation. Successful replacement of the external iliac artery in the case of aneurysm of this vessel has been reported by Swan [88], employing a preserved homologous artery graft.

Following ligation of the common iliac artery, the collateral channels are chiefly through anastomoses between the superior epigastric, lumbar, and intercostal arteries above with the deep iliac circumflex, the iliolumbar, and the inferior epigastric arteries below. The middle sacral and the ovarian or spermatic arteries contribute through anastomoses with branches of the internal iliac arteries inferiorly. There is also important collateral flow through the corresponding contralateral branches from the opposite internal iliac artery.

In the extensive dissection during hemipelvectomy it is desirable that control of blood loss be obtained through ligation of the external iliac artery performed as an initial step. However, ligation of the external iliac artery alone does not affect the blood supply from the parietal branches of the internal iliac artery that are encountered on division of the pubic and sacroiliac articulations and other structures deep in the pelvis. Early or preliminary ligation of the common iliac artery does, and provides a relatively bloodless field, so that it has been used by some surgeons. Necrosis of the posterior skin flap, however, frequently follows permanent common iliac artery ligation in this procedure. Temporary occlusion of the common iliac artery may be performed and should be done early in the operation. After division of the rectus abdominis muscle and the attachment of the inguinal ligament, the common iliac vessels can be exposed retroperitoneally. Healing per primum followed in three cases reported by Wise in which temporary common iliac artery occlusion was practiced [99]. Temporary ligation of the common iliac may be performed through a midline abdominal incision whenever preliminary abdominal exploration is indicated [47].

THE INTERNAL ILIAC (HYPOGASTRIC) ARTERY

The pelvic viscera are well supplied with blood vessels having a multiplicity of collateral connections. This abundance of vessels permits ligation of both internal iliac arteries with a high degree of safety. The internal iliac artery leaves the common iliac at its bifurcation, which overlies the sacroiliac joint. The internal iliac then descends into the pelvis for a short distance and thereafter divides to form two large trunks. These comprise the posterior trunk, which is distributed to the iliac, lumbar, sacral, and upper gluteal regions, and the anterior trunk, whose branches go to the bladder, rectum, vagina, uterus, and lower gluteal regions through the obturator canal. The routes for collateral circulation are too numerous to warrant description, especially since the internal iliac may be ligated without concern as to the adequacy of blood supply to the organs and tissues that it serves.

The patient with cancer of the cervix who, after receiving a maximal amount of irradiation, has serious hemorrhage may require bilateral internal iliac ligations. In certain patients in whom bleeding is severe, ligation of the ovarian arteries and of the vessels in the round ligaments may be advisable in addition to bilateral internal iliac artery ligations. In the radical operation for cancer of the cervix and in the operation of pelvic exenteration, ligation of both hypogastric arteries as an early or preliminary step is advised by some

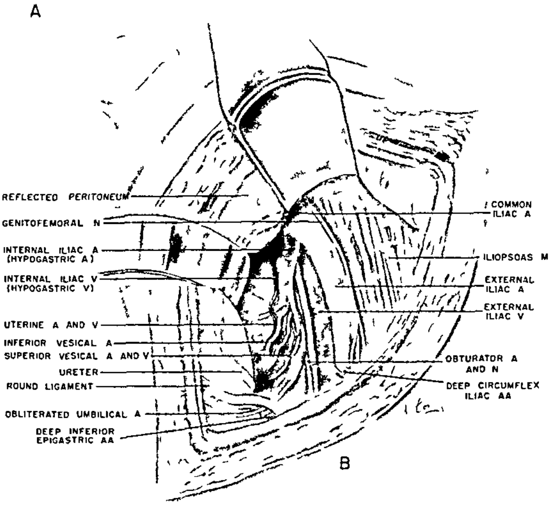


Fig 12 7 The extraper toneal approach for l gation of the internal l ac artery A The incis on is made 1 to 2 cm above and parallel to the ing inal ligament B Showing the exposure obtained after the per toneum has been reflected med ally from the l ac fossa a d pelv s Note the ureter adherent to the reflected per toneum

surgeons This step is especially valuable in the pelvic exenteration procedure There is less blood loss and a drier field for dissection is obtained During resection of the rectum and rectosigmoid for carcinoma, ligation of the internal iliac arteries may facilitate hemostasis in certain cases that would otherwise interfere with a satisfactory operation Hemorrhage from bladder cancers usually may be controlled by cystotomy but in some cases of extensive carcinoma this is undesirable Significant blood loss may occur the bladder fill with large clots, and urinary retention supervene Ligation of both internal iliac arteries is occasionally a useful procedure for controlling severe bleeding from bladder neoplasms particularly in cases that have had persistent bleeding following radiation therapy

The operative approach to the internal iliac arteries may be transabdominal during the course of intraabdominal surgery or through the bilateral extraperitoneal exposure The latter is probably less shocking to the debilitated and exsanguinated patient who might require the operation Within the abdomen the vessels are simply exposed by incising the pelvic peritoneum over them On the left the sigmoid mesentery must also be reflected toward the mid line In the extraperitoneal approach to the vessels an incision is made 1 to 2 cm above and parallel to the inguinal ligament from the level of the external inguinal ring up to the anterior superior iliac spine This approach is shown in Figure 12 7 The aponeurosis of the external oblique muscle is split and the incision deepened by dividing the internal oblique and transversalis muscle and fascia The iliohypogastric and ilioinguinal nerves are preserved as they are found with the internal oblique muscle The peritoneum is then pushed upward away from the pelvic wall to expose the external iliac vessels This maneuver is continued until the bifurcation of the common iliac artery is reached The deeper and more medial branch of the common iliac artery is the internal iliac artery This is readily distinguished from the external iliac artery that proceeds along the brim of the pelvis to pass beneath the inguinal ligament After dissecting the vessel free a ligature may be passed about it and tied It may be difficult safely to divide as well as ligate the vessel in this situation although adequate exposure should be secured to make it possible Ligation of the internal iliac vein may be safely done at the same time if need be Closure of the operative wound is simply achieved by allowing the peritoneum to fall back in place through the weight of the viscera above The musculofascial structures are approximated with interrupted sutures

FEMORAL AND POPLITEAL ARTERIES

Major artery ligations in the lower extremity are in general more hazardous than in the upper extremity as regards loss of the viability of some part of the limb Primary ligation of the popliteal artery is followed by a high incidence of severe arterial insufficiency with some gangrene resulting in about 75 per cent of cases The same unfortunate hazard follows ligation of the common or superficial femoral arteries Superficial femoral artery ligation carries a risk that is somewhat less The profunda branch of the femoral artery can be ligated without serious effect in most cases but it is rarely required The more distal tributaries of the popliteal artery the anterior and posterior tibial arteries of the lower leg can be sacrificed individually with impunity but with occlusion of both some loss of toes may result The especially high incidence of gangrene associated with popliteal and common femoral artery interruption is accounted for in part by the frequent injury to collaterals occurring when these arteries are wounded or operated upon

Anatomy The femoral artery lies relatively superficial in the femoral triangle and is closely associated with lymphatics that drain from the leg into the inguinal lymph nodes It is occasionally involved with primary or metastatic malignant tumors in cases in which radical dissection of the groin is undertaken Indeed at any point along their course the major vessels of the extremities may be so intimately involved with a soft tissue sarcoma that resection of a segment of the vessel is necessary if the tumor is to be entirely removed The successful implantation of artery and vein grafts in patients who have required

femoral artery resection because of neoplastic involvement has been reported by Swan The use of peripheral artery homologous grafts in this situation had been generally considered impractical until recently

When the common femoral artery is occluded the important collateral channels superiorly are through the tributaries of the superior gluteal the inferior gluteal and obturator arteries plus all branches of the internal iliac artery These vessels anastomose distally with the lateral and medial femoral circumflex arteries and also with upper branches from the profunda femoral artery In cases of superficial femoral artery interruption the principal connecting vessel between the upper femoral and the more distal arteries of the leg is the descending branch of the lateral femoral circumflex artery There are also anastomoses of the fourth perforating branch of the profunda femoris artery with the geniculate arteries about the knee Because of the absence of heavy musculature about the knee there is a lack of the small muscular arteries that can develop as effective collaterals [73] This deficiency is largely responsible for the dependency of the lower leg on an intact popliteal artery Collateral channels around the popliteal artery include the highest and the medial and lateral superior geniculate arterials which anastomose inferiorly with the medial and lateral inferior geniculate and anterior tibial recurrent arteries Some of the collateral flow from above comes via the fourth perforating branch of the profunda femoris artery and the descending branch of the lateral femoral circumflex as well These unfortunately comprise relatively few and small channels

Surgical Approach Good surgical exposure of the femoral artery may be obtained by means of a vertical incision placed over the artery in the femoral triangle This incision can be extended down through the adductor canal to the point at which the femoral artery pierces the adductor magnus muscle and becomes the popliteal artery The incision is made along a line extending from the midpoint of the inguinal ligament to the internal femoral condyle The sartorius muscle serves as a landmark since it forms the lateral boundary of the femoral triangle At the apex of the triangle this muscle crosses the vessels to lie superficial to them in the adductor canal In Hunter s canal just deep to the sartorius muscle is a dense aponeurosis that can be divided to allow further access to the vessels The profunda femoral artery leaves the common femoral artery posteriorly at its bifurcation about 1 5 inches from the inguinal ligament In the femoral triangle the femoral nerve lies lateral to the artery The vein lying first medially gradually assumes a posterior relationship to the artery, which it retains as it continues through the adductor canal

The popliteal artery may be approached at its origin medially just as it leaves the adductor canal to pass into the popliteal fossa through the tendinous hiatus of the adductor magnus muscle The incision is made just anterior to the adductor tubercle of the internal femoral condyle and is carried upward The leg is maintained in an abducted and everted position with the knee flexed which relaxes the musculotendinous structures so that the popliteal space opens up The artery presents itself upon posterior retraction of the medial hamstring muscles and tendons together with the saphenous vein The more inferior portion of the popliteal artery is be[illegible] exposed through a vertical incision posteri[illegible] over the popliteal space This incision is be[illegible] when made in a modified S shape wit[illegible] transverse component along the line of [illegible] flexion crease in order to avoid a contr[illegible] scar [22] The lesser saphenous vein [illegible] as a guide through the deep fascia [illegible] the popliteal vein in the fossa whe[illegible] lateral to the popliteal artery On[illegible] occasions arise for exposing th[illegible] artery in the surgery of malignan[illegible]

Interruption of Important [illegible]

Throughout the body the [illegible] channels are larger more pl[illegible] adequately supplied with c[illegible] the major arteries Almos[illegible] bilateral may be interr[illegible] without appreciable dele[illegible] only minor disability Th[illegible] venous channels that [illegible] arranged or that drain [illegible] cannot be safely lig[illegible] are the inferior ve[illegible]

veins the superior mesenteric vein, the portal vein and the superior vena cava All these veins normally lack established or potential collaterals of sufficient size to prevent severe congestion of important viscera when they are suddenly occluded—an occurrence that may lead to rapid death A gradual occlusion on the other hand may be sustained by producing slowly developing hypertension in the venous bed which stimulates the opening of collateral routes The extensive collateral circulation that develops between the portal system and systemic veins in cases of cirrhosis of the liver is an example of this phenomenon Ligation of the portal vein in cases of severe portal hypertension is not fatal when extensive esophageal varices and other collaterals have developed

THE VEINS OF THE EXTREMITIES

Edema of tissues peripheral to the point of ligation of major extremity veins often occurs It is not always possible to ascertain the role of venous stasis itself in the causation of the edema Blockage by inflammatory fibrosis of lymphatics accompanying the veins has been ascribed as an important factor in its production

Also of importance is the functional state of the remaining collateral veins with respect to their occlusion by thrombosis or incidentally at operation The large number of individuals who have had their superficial and common femoral veins ligated in the treatment or prophylaxis of deep venous thrombosis without sustaining disabling sequelae attests to the safety of ligating the large veins of the lower extremity Edema however is often a persistent complication of common femoral vein ligation The studies of Homans [39] demonstrate that ligation of the common iliac vein results in better collateral circulation than ligation of either the external iliac or common femoral vein There is also little difference between the effects of ligating the inferior vena cava or both common iliac veins

In the upper extremity the main veins can apparently be ligated with the same freedom MacDonald has adopted a policy of resecting the axillary veins in the course of radical mastectomy when axillary metastases are apparent In doing so he makes an effort to preserve the cephalic vein The occurrence of lymphedema in a small series of such cases reported by him is no higher than customarily occurs when the vein is left intact

THE JUGULAR VEINS

The unilateral resection of the internal jugular vein and the external jugular vein in the operation of radical neck dissection has long been recognized as being without serious effect There has been however considerable hesitancy on the part of many surgeons in subscribing to the sacrifice of these vessels in both sides of the neck Where the usual neck dissection might have been indicated on the second side it has often been modified with preservation of the internal jugular vein and frequently surgery has been abandoned in favor of radiation therapy Recent reports by several observers support the practicability and the safety of complete bilateral neck dissection with bilateral jugular occlusion as carried out in two stages Martin *et al* have had no postoperative deaths in 66 patients with bilateral procedures and in 50 cases with histologically proved bilateral metastases have had 5 year cures in 30 per cent

An excision of the entire internal and external jugular veins along with other veins included in the radical neck dissection eliminates a much larger part of the potential venous collateral channels than does simple ligation Yet adequate routes of egress for venous blood from head and neck appear to be available even to allow at least in some cases one stage jugular occlusion without 2 to 3 weeks elapsing between stages

Attention has been directed by Batson to the richness of the pathways of venous drainage from the region of the head There are abundant communications between the intracranial and interosseous and extracranial portions of the venous system about the head Valves are virtually absent except in the distal part of the internal jugular veins so that retrograde flow readily occurs throughout the system Important venous collateral pathways in the flow of blood from the head with bilateral jugular occlusion are the deep posterior cervical collecting veins such as the vertebral occipital and deep cervical veins

the pharyngeal pterygoid and esophageal venous plexuses and of much importance the vertebral venous plexus The vertebral system of veins consists of both an internal and external plexus of veins with respect to the spinal canal These have many intercommunicating veins and at each intervertebral space there are anastomoses with veins of the neck thorax and abdomen This provides free communications with the systemic venous system to such an extent that on straining or coughing blood may be diverted into the vertebral venous plexus from peripheral parts of the body [4]

Bilateral removal of the jugular veins does result in partial venous stasis about the head Gius has described consistent clinical manifestations of this condition which include a varying degree of edema rapidly appearing about the face in all cases The edema gradually subsides though not completely in some cases Immediately following ligation of the second internal jugular vein the face assumes a pink or cyanotic hue that subsides more rapidly than does the edema A severe headache may be present after operation and this lasts as a rule for several days It tends to recur if the head is placed in a dependent position so that most patients prefer to sleep with their heads elevated There has been found no evidence of serious alteration of the cerebrospinal fluid pressure and no visual disturbances or persistent eye ground changes have followed bilateral internal jugular vein ligation Neither Gius nor Martin reports any mortality in the immediate postoperative period following bilateral ligation If laryngeal edema even of mild degree is present when bilateral ligation is anticipated tracheotomy is probably advisable

THE INFERIOR VENA CAVA

Numerous clinical observations have demonstrated that sudden complete ligation of the inferior vena cava in its lower one third below the renal veins is compatible with life being tolerated and scarcely causing any circulatory difficulties in the majority of cases As might be expected edema of the lower extremities is the chief sequela In most cases the edema is transitory and disappears after 6 to 10 weeks though in elderly individuals the edema tends to persist to some degree With adjustment of the venous return through collateral development the appearance of hemorrhoids and varicosities about the genitalia and lower abdomen have been noted to follow inferior caval ligation The absence of signs of venous vascular disorder is accounted for by the multiplicity of collateral channels available after ligation of the inferior vena cava at this level The principal collateral veins have been shown to be the veins of the pelvic and abdominal walls the veins of lumbar and azygos systems the vertebral plexus of veins and the portal venous system These various groups intercommunicate either directly or indirectly Of less importance are the superficial veins of the trunk [77]

Inferior vena cava ligation is not entirely without hazard In certain cases ligation of the inferior vena cava below the renal veins has not been tolerated because the available collateral routes were insufficient A condition of acute venous congestion ensues that has in some instances terminated in gangrene It seems to be most commonly associated with obstruction of the deep veins of the leg by thrombosis The legs become cyanotic and tensely engorged with blood and petechial hemorrhages occur If the patient is conscious severe pain may be expected Shock may develop Some indication of the adequacy of collateral venous circulation can be obtained at the time of ligation by the extent of drop in blood pressure If severe hypotension persists in spite of adequate transfusion the ligature must be removed and the procedure abandoned The vena cava should be temporarily occluded before applying the final ligature to determine the effects of ligation The operation should never be concluded until the ligation has proved to be well tolerated as evidenced by absence of or recovery from shock and the extremities should neither be cyanotic nor engorged In the event that the patient is found to have an inadequate collateral circulation the treatment for this condition is release of the ligature or if this is not possible because of the lapse of time since ligation and the poor state of the patient the only effective treatment is elevation of the leg and exercises [93] This maneuver consists in actively flexing and

extending both legs continuously until the condition improves Elevation is then continued Such exercises 'pump blood out of the leg through small channels that will eventually take over the burden of collateral circulation

There is general agreement that ligation of the inferior vena cava above the level of the renal veins is incompatible with life Renal engorgement sufficient to produce complete shutdown occurs if the inferior vena cava is completely occluded for more than 10 minutes above the renal veins In the operations for anastomosis of the portal vein to the vena cava above the renals, only a portion of the wall of the cava is included in a special clamp Free flow beneath this pinched off segment allows normal renal venous drainage so essential to a safe operation Should the vena cava above the renal veins be occluded generally as is found in some cases at operation, good collateral would be present permitting resection of that part of the vessel Resection of the vena cava under such circumstances would rarely be indicated Resection of part of the wall of the vena cava above the renals repairing and creating a narrow but adequate channel has been done in cases of local tumor involvement without renal impairment

THE SUPERIOR VENA CAVA

Interruption of the superior vena cava causes severe symptoms and disability Even when the collateral circulation is fully developed there is as a rule rather poor compensation In patients who have survived superior vena cava ligation there is often edema of the upper part of the body and pleural effusion In the dog Carlson found that acute occlusion of the superior vena cava below the azygos vein was fatal while ligation above the azygos vein allowed the survival of six out of seven animals More serious consequences can be presumed to occur in man Animal experiments of Gerbode *et al* in which the azygos vein was anastomosed above the site of superior vena cava ligation and in which the divided superior vena cava was successfully anastomosed to the right auricular appendage when vena caval ligation was done below the azygos suggest that the superior vena cava can be resected successfully in man if suitable anastomoses can be made reconstituting channels for the return of blood to the heart Vein grafts might prove useful for this work

THE PORTAL VEIN

The painstaking effort necessary for the preservation of the portal vein has been accepted as essential in the operation of radical pancreaticoduodenectomy for carcinoma of the head of the pancreas That the portal vein must be saved is a recognized defect in the operation Dissection of the pancreas from the vein with an invasive cancer only a few millimeters away is far from ideal as a principle of radical cancer surgery If the vein wall is invaded the situation is unfavorable for excision It must be accepted that the small intestine becomes engorged with blood that cannot escape from it if the portal vein is interrupted The results of sudden portal vein occlusion as studied in animals depend upon the particular species Such an event is fatal for the cat rabbit and dog It is fatal in man unless gradual occlusion with some degree of portal hypertension followed by development of adequate collateral routes has occurred Portal vein ligation is well tolerated in Rhesus monkeys Child [13] has found that monkeys can tolerate the circulatory adjustment necessary for survival after portal vein resection en bloc with the lower part of the stomach Portal venograms of ligated humans and monkeys are similar However the monkey has a more adaptable collateral system since it does not develop portal system hypertension as does man with portal vein obstruction Child reports ligation of the portal vein in two patients who had non resectable cancer who survived for 2½ and 8 months respectively Parsons describes two cases one of partial and one of complete portal vein resection with survival in instances where the vein was involved by tumor DeBakey describes a case in which a segment of superior mesenteric vein was successfully resected along with a mycotic aneurysm of the superior mesenteric artery These cases demonstrate that at least in some instances of sudden interruption of the portal or superior mesenteric veins adequate collateral circulation may exist It is a reasonable pre

sumption that in certain cases of extensive cancer of the pancreas or stomach in which long standing disease has partially obstructed the portal vein some degree of portal hyper tension gradually develops and in a few cases adequate collateral channels are present Whether or not diversion of portal blood into the vena cava by anastomosis of the superior mesenteric vein to the inferior vena cava (essentially an Eck fistula) will ever be possible in human subjects with removal of the portal vein remains to be seen The operation is feasible using venous grafts but there are so many technical difficulties that it may be impracticable The preliminary step of gradual occlusion of the vein before re section in the attempt to accelerate collateral venous routes is also not practicable While spleno renal anastomosis is another theoretic means of decompressing the portal system before pancreatic resection it has not been tried The objection to preliminary venous shunting of the portal system is that such anastomoses would be likely to close in the absence of portal hypertension More exten sive resections about this region of the hepatic pedicle must be devised if cancer of the head of the pancreas cancer of the bile ducts and extensive gastroduodenal cancer are to be more adequately treated Progress in vascular surgery and particularly in vessel replacement by autografts or homografts is essential to this enterprise

TECHNICS IN VASCULAR SURGERY

The Temporary Occlusion of Vessels

In order to perform a reparative or recon structive procedure on a blood vessel com plete control over the blood flow within it is essential This requires an adequate exposure of the region being operated upon and a reliable means of temporarily occluding the vessel Many special occlusive vascular clamps and technics have been developed over the years Recent progress in the surgery of con genital heart disease and other operations involving the great vessels has resulted in the development of new instruments De scriptions of some of these instruments are included here because they can often be used to advantage in situations other than those for which they were originally designed At operation when no special vessel clamps are available, workable improvisations may be quickly applied

SPECIAL INSTRUMENTS FOR VASCULAR SURGERY

In Figure 12 8 instruments useful in vascu lar surgery are shown In addition improvisa tions of vascular instruments made from readily available materials are described The serrefine or bulldog clamp is the standard vessel occluding instrument It is effective in occluding vessels the size of those in the upper or lower extremity It is not sufficiently secure for the larger arteries such as the iliacs for vessels of this size a clamp that locks is desir able The serrefine may be used either un covered or shod with rubber or shoe lacing The latter covering is less apt to permit slip ping of the clamp on the vessel The tension of each serrefine as used on a particular vessel should be tested and adjusted for adequate tension without too great crushing strength

The Blalock clamp is excellent for oc cluding large vessels either arteries or veins It permits an accurate adjustment of pressure on the vessel wall and a means of locking the clamp It is best used uncovered A clamp that does not slip longitudinally on the vessel permits the approximation of the retracted vessels The clamp described and employed by Potts [71] for the division of the patent ductus arteriosus finds uses on other vessels where slipping of the clamp during approxi mation is undesirable Potts ductus clamp has a series of fine sharp teeth along its jaws that bite into the adventitia of the vessel and prevent slipping yet do not significantly damage the vessel wall If the need for tem porarily occluding an artery arises when special vessel clamps are not readily avail able several technics may be used instead The simplest of these is to occlude the vessel with a tape snugged up by means of a hemo static forceps For prolonged clamping when the forceps would be in the way the oc cluding tape may be secured by tying it with heavy suture material Another convenient method is carried out by passing a tape about the vessel and passing it through a glass or rubber tube The vessel is obstructed by pull

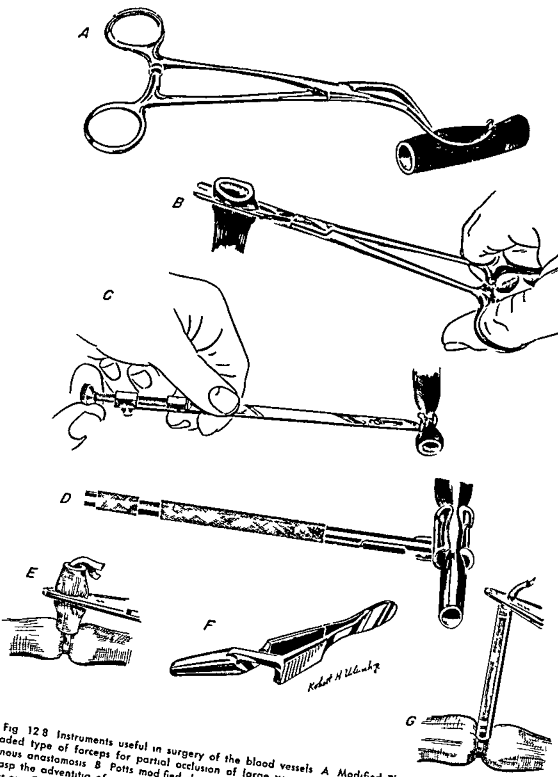


Fig 128 Instruments useful in surgery of the blood vessels A Modified Thomas Smith clamp A spring bladed type of forceps for partial occlusion of large veins such as the vena cava Useful for end-to-side venous anastomosis B Potts modified ductus clamp The many opposing fine teeth (40 to each inch) firmly grasp the adventitia of vessels and prevent slipping Judgment must be exercised in closing jaws to proper tension C Blalock clamp Pressure is adjusted by a screw and locked by a second screw This clamp is useful for larger arteries and veins especially in deep cavities D Potts Smith clamp Used when part of occlusion only is desirable as in the case of the aorta Blood flow continues through the cylindrical portion of clamp E Improvised method of arterial occlusion employing rubber tubing The tape is held tight by clamping through tubing F Serrefine or bulldog clamp Standard occluding spring type of clamp for medium or smaller sized arteries and veins G Improvised method of arterial occlusion A tape is looped through a glass tube and clamped after tapes are tightened

ing on the tape loop and then clamping the tape at the outer end of the glass tube or through the wall of the rubber tube This may be easily applied to the aorta For the aorta or the vena cava above the renals it is usually mandatory only partially to obstruct the lumen while carrying out an anastomosis This can be successfully accomplished in the aorta by means of another clamp devised by Potts and Smith for the operation of anas tomosis of the arch of the aorta to the left pulmonary artery in congenital pulmonic stenosis A segment of the thin wall of the inferior vena cava may be partially occluded by a curved spring blade intestinal clamp (Thomas Smith) as applied by Welch in portal caval anastomoses

The Division and Ligation of Large Vessels

The ligation of large vessels is not with out risk from late erosion of the vessel wall and hemorrhage Division and ligation of large vessels is preferable to ligation per formed in continuity It is safer because in the divided vessel the pulsatile force does not act upon a fixed point and the elastic longitudinal extension and retraction reduce the force of pulse wave at the site of ligation Small or medium sized arteries and veins however can be safely ligated in continuity with a single interrupted ligature On sizable vessels ligatures should be re enforced to prevent their slipping off This is best done by means of a transfixion suture ligature placed immediately distal to the first tie It was advocated by Ballance and Edmunds that larger arteries should be tied just firmly enough with heavy double ligatures only to approximate the intimal surface and avoid fracturing the arterial wall Halsted pointed out that ligatures are usually applied too quickly before healing has given the vessel enough strength A similar principle applies to the use of transfixion sutures If the suture is placed at any distance from the proximal ligature the intervening segment may become necrotic and the ligation as a whole will be weakened Reid has stressed the advantage of having the vessel segment undergoing ligation relaxed and empty of blood during the act of ligating larger arteries The ligature can then be set down with the proper tension and there will be less likelihood of cutting or fracturing the vessel wall Early dissolu tion of ligatures is dangerous and may release a necrotic vessel well before strong healing has been secured Halsted re emphasized the desirability of using nonabsorbable ligature material on arteries in preference to catgut for this reason Because fine ligatures tend to cut through the vessel wall faster than larger ones Reid advised that the size of ligature material be increased in proportion to the size of the artery He suggested that a single strand of braided silk be used for tying an artery the size of the radial For vessels the size of the femoral artery or the subclavian artery two strands of heavy braided silk should be used For ligating the iliacs or the aorta 2 and 3 strands re spectively of braided tape should be applied For arteries ligated in continuity heavier material should be used than when vessels are interrupted These principles are sound even though the factor of infection has been largely eliminated in present day surgery and the difficulties with ligature erosion have been lessened It is impractical to give exact speci fications for the size the type and the number of ligatures to be applied in a given case for any vessel Suture closure of the end of a large divided artery is preferable to the en circling ligature especially when only a short segment is available for ligation (Figure 12 9) Swan and Harper have demonstrated its efficacy in experimental studies on the dog s aorta The closure of the end of the artery is accomplished by a continuous double crossed stitch such as used by Gross and by Linton on the popliteal artery

When large veins are divided care must be taken to avoid the sucking of air into the vessels Fatal air embolism may result This is liable to occur particularly in the neck where the vein may be partially held open by surrounding fascial tissues The slight negative intrathoracic pressure present during inspiration and transmitted to the vessels entering the thoracic cage is respon sible

The Gradual Occlusion of Large Arteries

Many ingenious technics for producing gradual occlusion of large arteries have been

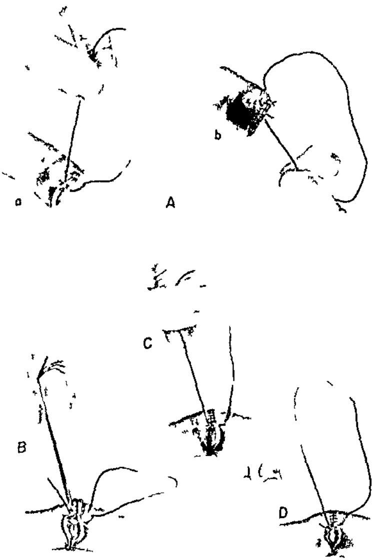


Fig 12 9 Arterial suture technics A Suture closure of the end of a large divided artery First row of simple over and over whip stitch (a) followed by a continuous suture and (b) carried back as a second cross ng row B Interrupted mattress suture The edges are everted with intima to-intima approximation Minimal suture is exposed within the lumen C Continuous through and through suture including all layers There is end to-end layer approximation D Continuous through and through suture avoiding the intima Essentially no suture material is exposed in lumen and end to-end layer approximation is obtained

devised over the years Metal clamps or bands and tissue strips have not been successful either because of failure completely and permanently to occlude the vessel or because of the resulting pressure atrophy of the arterial wall Rupture and hemorrhage have frequently followed their use Dilatation and thinning of the wall beyond the stenosis also occur Even gradual occlusion by means of broad cone shaped elastic bands is accompanied by a prohibitive occurrence of hemorrhage [64] Methods of occlusion by intraluminal obstruction have been tried Rolls of fascia sutured within the vessel (Reid) small coiled wire springs threaded into the aorta (Pearse), and infolding plication by suture

of the arterial wall have all failed to provide uniform effective and well controlled occlusion Certain irritating plastic materials of the cellophane or polyethylene types have been found to provoke an intense fibroblastic reaction sufficient progressively to constrict large vessels and completely occlude them when applied to their exterior (Pearse) The irritant properties of these plastic substances have been found to be due to an adulterant dicetyl phosphate present in just those prepared by certain processes [100] Experimentally in the dog s aorta fibroblastic irritants have been effectively combined with a partially occluding metal band of tantalum for producing occlusion [14] These methods all are at a disadvantage in cancer surgery since they require a long period of time (two months or more) to achieve the desired occlusion Fibroblastic agents also provoke a reaction in the surrounding tissues that is a hindrance in dissection

The Anastomosis of Blood Vessels

Careful technic is essential for the successful performance of a vascular anastomosis Vessels and segments of vessel grafts must be handled gently so as to avoid injury Drying of the vessel should not be permitted During the anastomosis procedure good hemostasis both about the wound and within the vessel lumen is mandatory in order to avoid the formation of small thrombi at the anastomosis from which larger clots form after the flow of blood is restored The anastomosis that is smooth with few irregularities or constrictions within the lumen insures a smoother more streamlined nonturbulent flow of blood and is more likely to remain patent Strict asepsis must be observed to minimize the chance of local wound infection that may lead to thrombosis or hemorrhage After the completion of anastomosis blood flow should be maintained in good volume at a good pressure The likelihood of thrombosis occurring at the anastomosis is increased by any restriction of the blood flow through it Conditions that contribute to impaired flow at the anastomosis include segmental arterial spasm hypotension and generalized reflex vasoconstriction that occurs with shock Attention must be given to the correction of such abnormalities

ANTICOAGULANTS

It is well established from experimental and clinical results that satisfactory blood vessel anastomoses even in arteries as small as 3 5 mm to 4 5 mm in diameter can be successfully performed without an important incidence of thrombosis even though anticoagulants are not used [60] In larger vessels thrombosis is less likely to occur Heparin and Dicumarol therapy for rendering the blood incoagulable on other accounts than to prevent thrombosis at an arterial anastomosis have been extensively applied in the prophylaxis and treatment of spontaneous intravascular thrombosis As a general rule it is safe to say that generalized anticoagulant therapy either during operation or after operation is unnecessary and may even be undesirable when vascular anastomoses have been made An adequate volume of blood flowing freely through the anastomosis can be considered to be the best safeguard against thrombosis If anticoagulants are to be used the time when it is safe to start their use is determined by the nature of the operative procedure The most critical period for formation of a thrombus is immediately following completion of the anastomosis and ideally an anticoagulant would be most effective if given at once In the extremity where hemorrhage can be easily recognized and controlled anticoagulants may be safely given preoperatively It is not safe however to have an early anticoagulant effect when procedures within the body cavities have been performed The administration of anticoagulants must be delayed in such cases until bleeding may be assumed to have stopped by spontaneous coagulation in the area of the wound A delay of 2 to 4 hours following operation is considered sufficient by some The prevention of thrombosis by anticoagulant therapy during the first day or two after operation does not preclude its occurrence after anticoagulant therapy has been discontinued The possibility of thrombosis occurring in an anastomosis exists from 2 to 3 weeks after operation until healing of the vessel is complete

In the selection of an anticoagulant drug

vein covered rigid metal cylinder is then inserted into the lumen of the recipient vessel where it is secured in place by an encircling ligature An intima to intima type of anastomosis, with no suture material exposed in the lumen can be performed by this technic It forms a leakproof joint It may be used for an end to side vein anastomosis by inserting the vein cuffed tube through an opening in the wall of a large vein such as the vena cava and holding it in place with a purse string type of suture A vein graft may be inserted by cuffing each end of the graft with a metal tube and completing the anastomosis with the divided vessel ends in the same way attention must be given to align the valves in the graft with the direction of blood flow The method is one of seeming simplicity not requiring meticulous suturing yet to the unpracticed it presents many technical difficulties The metal tubes must be just the proper size If too large the tube cannot be inserted in the open receiving vessel, even though it is held open and triangulated by fine forceps If the receiving vessel is in spasm this is especially difficult The anastomosis has the disadvantage of being somewhat constricted by the permanent rigid ring This constriction causes turbulent blood flow which predisposes to thrombosis particularly in small vessels In some instances the vessel wall has been eroded by the metal tube, which has acted as a metallic embolus within the lumen in others the tube has been extruded outside the vessel to cause severe hemorrhage The complications with this technic are more frequent than with a well done suture anastomosis It should be used only in special instances and never as the method of first choice

ARTERIAL GRAFTS

When vessel ends can be approximated for anastomosis without undue tension grafts are not necessary However in the presence of obvious vascular loss or when there is tension at the suture line the suturing is more difficult and hazardous The vessel under tension becomes narrowed at the anastomosis by the stretching In cases in which a sizable segment of an important vessel is destroyed or resected replacement is the only satisfactory solution The recent clinical use of vessel grafts after extensive laboratory proving has demonstrated the value of both arterial and venous grafts in replacing arterial segments [32, 43, 88] Autografts are physiologically the most sound graft It has been shown that they survive as living vessel segments The lack of their availability is their principal drawback To obtain useful autografts entails sacrifice of an artery of comparable size which in the case of larger arteries cannot generally be done without jeopardizing the blood supply to other parts of the body Fortunately, arterial homografts have been found satisfactory and their application has developed beyond the experimental stage Both fresh and preserved homografts serve well, implanted as functioning segments of arteries The gross and histologic changes in the fresh homograft and the homograft that is preserved within certain time limits are similar [59] Studies of the changes indicate that a homograft eventually dies but as this occurs the medial layer of the graft undergoes a collagenous alteration becoming eventually an acellular layer of good strength The intimal layer necroses but is replaced by a fibrocellular layer The sutures at the anastomosis are covered by this tissue also The homologous type of graft has been shown to be satisfactory for arteries as large as the human aorta and as small as the femoral artery of the dog of 3 mm to 4 5 mm in diameter

Like autografts fresh homografts are not always readily available and to have them at operation demands some method of preservation from the time they are taken until they are used The experimental studies of Gross and his associates [32] have proved that arterial segments can be taken from 4 hours to 5 hours after death and preserved for 35 days to 40 days before use Tissue cultures at that time show viability of at least certain types of cells It is generally believed that viability of the tissues is desirable at the time of implantation and these time limits are generally accepted at present Some work with small arteries suggests that there is an increased occurrence of minor defects after 1 to 2 weeks storage and perhaps small arteries should not be used after 10 to 14 days banking for best results [59]

Several satisfactory methods of preserva-

tion and storage of grafts have been used The method developed by Pierce Gross *et al* has been most extensively used The preserving medium is a modified type of Tyrode electrolyte solution that is buffered and to which has been added 10 per cent homologous serum 1 per cent dextrose and penicillin and streptomycin 50 units for each cc It also contains an indicator to show pH changes The arterial segments are covered with this liquid and stored in sealed bottles at refrigeration temperatures between 0° C and 4° C Another method of preservation is a quick freeze technic with storage of the grafts at lower temperatures While methods of this type have not been as extensively applied in clinical work as those employing the physiologic solutions good results have been reported by Blakemore *et al* Hufnagel and Deterling *et al* This method of preserva tion and storage of grafts seems to hold out the best hope for storing grafts for longer periods of time The preservation of arterial grafts by the freeze drying method whereby homografts are quick frozen and lyophilized has been found to be successful [54] This technic produces dehydrated grafts that may be stored at room temperature for indefinite periods of time

Grafts of dogs aortas that have been de vitalized by formalin fixation have been im planted in animals with satisfactory results though the morphologic alterations in the grafts were found to be more severe than in the living type of graft The possibility of using heterografts between differing species has also been experimentally investigated with inconclusive results

The procurement of suitable human arterial vessel segments for homografts presents prob lems because of scarcity of suitable material It is impractical for one institution to bear the trouble and expense of maintaining its own bank Even large institutions require grafts too infrequently to maintain a reasonably complete bank It is desirable to establish a central depot or bank in large cities or geo graphic regions with a group of hospitals contributing After this is established the sur rounding smaller neighboring communities may be supplied Such a central bank has been established and has been in operation for a short time in New York City [44]

VEIN GRAFTS

The disadvantage of the limited availability of the arterial graft may be resolved in the individual case by the use of autogenous vein grafts for replacing arterial segments There are many veins of suitable size that can be removed from the same individual without risk of serious difficulty Recent experimental work and clinical reports of their use in arterial injuries congenital defects and aneu rysms have been encouraging [43] The vein graft presents some inherent disadvantages It is soft and pliable and tends to collapse during the anastomosing and is therefore not as easy to handle as an artery with its more rigidly maintained lumen It is also somewhat difficult accurately to match the diameters of vein grafts and the recipient arteries Dilata tion of the implanted segment takes place under arterial pressure Although aneurysm formation is not marked there is a degree of dilatation at the region that creates turbulent blood flow and is more likely to result in thrombosis under adverse circumstances Ar terialization of the wall of the vein graft implanted in an artery has been described Johnson and Kirby in their studies found that the gross thickening of the wall of vein grafts occurring progressively represented a fibrosis characteristically involving all layers of the graft wall

Either the nonsuture or suture technic of anastomosis is applicable to the vein graft The suture technic is preferable In perform ing vein graft anastomosis care must be exercised to place the vein segment so that its valves do not obstruct the flow of blood Veins available for use are the greater and lesser saphenous veins the femoral vein or its branches and perhaps the iliac veins

INERT PROSTHESES

Many substances have been employed as vessel prostheses These include tubes of silver of glass coated with paraffin vein lined vitallium tubes and more recently various plastic materials Some of the plastic materials employed experimentally seem to function well for relatively long periods in the aorta

In smaller vessels they have not been at all satisfactory [10] Hufnagel has implanted highly polished methyl methacrylic tubes in the dog s aorta These have remained function ing for periods over a year He has also de veloped a technic for implanting a graft seg ment in the aorta that avoids the effects of prolonged vessel occlusion ordinarily required for such an arterial anastomosis [42] This is accomplished by placing within the graft a polished plastic tube that serves as a temporary bridge for blood flow during the suture pro cedure This tube is held in place by ligatures at either end after it is inserted in the open ends of the divided aorta The graft segment is sutured in place completely at one end and only partially around the posterior aspect at the other Sutures are placed anterior at this end but not tied The plastic tube is then released slid upward and then down and out through the half closed distal anastomosis The anastomosis is then closed by rapid tying of the stitches and blood flow is shortly re sumed

The use of inert substances as permanent prostheses now seems practical in the aorta and large vessels Grafts made of vignon nylon and other plastic textiles can be tailor made to size in the operating room Patterns are made by the surgeon and are given to a nurse, who can quickly make a simple tube or Y shaped cloth graft using a housewifes sewing machine These grafts bleed" when first put in place but clot soon closes their pores Endothelialization later occurs by the adaptation of fibroblasts to this function Tex tile grafts seem to be the answer to replace ment therapy because of their availability and the fact that accurate sizes can be made for the vessels involved Present evidence seems to indicate that for large vessels they function as well as homografts and perhaps are supe rior The question of how well they will function in small arteries is not yet answered It is quite possible that textiles as grafts may be successful over long periods of time in the femoral popliteal and carotid arteries Auto-genous vein grafts however are perhaps the better choice at present In the next few years a wider application of some of the new technics developing now in the surgical re search laboratories will answer some of these problems in the use of prostheses as vessel grafts

Irradiation

CHAPTER 13

The Physical Basis of Radiation Therapy

Elizabeth F Focht
and
Edith H Quimby

All the natural sciences must follow carefully in the footsteps of arithmetic Radiotherapy as a science requiring as it does the viewpoint of the natural philosopher the three dimensional shape building of the geometer and the incessant number keeping of the arithmetician must effect the alliance of the radiologist and the physicist

The physicists have set up teaching programs especially during the last ten years to help the medical doctor gain a comprehension of yet another science and technic that of radiologic physics Since the last edition of this volume many physics texts have appeared that give a simple and complete understanding of the theory and principles of the physics of radiation therapy They include data for many of the dosage calculations with x ray and radioactive materials To repeat all that here would be almost as redundant as to include a chapter on anatomy

The following will recount the scope of the field in general and summarize the use of physical principles instruments gadgets and methods in most of the practical everyday use of x ray and radioactive materials for treatment Mention will be made of some of the other recent or possible future sources of radiation and references given to some of the texts from which in turn previous publications may be found

Nature of Radiation

The term radiation has come to include two somewhat different concepts Under various stimuli atoms may break down with the violent ejection of electrons neutrons or positive particles Charged particles may also be set in rapid motion in a vacuum under the action of electric and/or magnetic fields

Besides this particle type of radiation there is that known under the general heading of electromagnetic waves X rays and gamma rays together with visible light heat and radio waves are all part of the electromagnetic spectrum That is to say they are all manifestations of a propagation of energy that may be described as a wave motion They all travel in vacuum with the same speed but their wavelengths and frequencies differ enormously

Some of the phenomena of this electromagnetic spectrum cannot be described by the wave theory Then the radiation must be considered as particles or small bundles of energy called photons each of which has its quantum of energy

Passage of Radiation Through Matter

A beta particle or electron impinging on matter may traverse the interatomic spaces for some distance before interacting with a nucleus or much more frequently another electron It may lose its entire energy or only a part and be more or less widely deflected from its original direction After these encounters it may even be traveling in the opposite direction It will eventually be slowed down to the point where it can no longer remove an orbital electron or cause ionization For each type and each energy of high velocity particle there is a certain thickness called the range of any material that will just stop all the particles

Photons of x or gamma radiation may be imagined as behaving in a manner similar to beta particles Some will go through the interstices between atoms and emerge unaffected on the other side of a thickness of matter But most of them will sooner or later interact with an electron or, very rarely, with a nucleus When a photon interacts with an electron, the entire energy of the photon may be transferred to the atom the former ceasing to exist In this case an electron will be ejected from its atom with a high velocity and is termed a photo electron The remaining atom will emit a fluorescent or characteristic x ray

On the other hand the original photon may give up a small part of its energy to an electron and be itself deflected, then it is called scattered radiation The electron is known as a recoil or Compton electron The photon which now has less energy and a longer wave length will continue undergoing other collisions until it finally is used up, or completely absorbed At energies above one mev the photon may produce a positron electron pair and be itself absorbed in the process The fraction of the incident radiation entering into these phenomena depends on the energy of the x rays or gamma rays and on the elements *irradiated*

Ionization

When an atom has lost an orbital electron it is in an abnormal state electrically that is it has a net positive charge In this state it is said to be ionized or to be a positive ion The removed electron or any molecular aggregate to which it may attach itself is the negative ion A direct action of radiation on matter is to ionize some of its atoms Alpha particles being relatively large and heavy are powerful ionizers as they tear their way through substances Beta particles are also efficient ionizers The actual number of ions produced by encounters with photons is relatively small but the photoelectrons and recoil electrons which they produce are the same type of ionizers as are the beta rays

The distribution of ions within irradiated matter depends to a considerable extent on the type of radiation impinging on it For any particular atom the state of ionization does not last more than a small fraction of a second it attracts a negative ion, charges (or electrons) are interchanged and each returns to its neutral condition this phenomenon being known as recombination However during the time that the atom is ionized it is capable of entering into various chemical reactions if other conditions are appropriate The roentgen is defined on the basis of ionization in air but the ionization produced by 1 r in some substances such as a gram of bone may be much greater for some qualities than that produced in a gram of muscle

THERAPEUTIC APPLICATIONS

The purpose of radiation therapy is to produce some change in cell structure or activity—in the extreme case to kill it It is generally conceded that this is brought about by an effect on the cells themselves and on the tissue immediately surrounding them Such an effect must be due to ionization produced in and near the cell components by the action of the rays It has been shown that the degree of ionization produced is directly proportional to the amount of radiation delivered that is the energy absorbed for a given substance and quality of radiation Up to a certain region the greater the ionization the *greater the biologic effect*

In order to specify the energy absorbed and because of difficulty in measuring the dose according to the definition of the r at very short wavelengths the unit of the rad is much more useful where 1 rad equals 100 ergs per gram To utilize radiation therapy to the best advantage it is essential to find out how much radiation may be expected to produce a given effect and then to devise means for delivering this quantity to the tissues in question and at the same time for protecting other structures

It is usually true that different points in an irradiated mass do not receive the same amount of radiation this is inevitable when interstitial sources are used If regression of the tumor depends on every point within it receiving at least a certain minimum quantity then it is necessary to know the least dose delivered to any part of the mass This minimum dose should be taken into consideration in any discussion of radiation therapy It is of interest to know the amount of radiation leaving a radioactive source because other

things being equal the strength of the source determines the time of treatment It is important to know the amount falling on the skin since in many cases skin tolerance limits the amount of radiation that can be administered through any one field Neither of these is however of much value without the knowledge of the amount actually reaching the cells to be affected

Two general methods are used for the administration of radiation the external and the internal The first comprises all cases in which the source of radiation is outside the body Such are practically all x ray treatments and the application of radium or artificially produced radioactive isotopes by means of telecurie units packs plaques or moulages In the second the source of radiation is buried directly in the tissue to be treated or inserted in the body cavities

The two obvious differences between these methods are (1) In external irradiation only a small part of the available energy actually reaches the tissues Radiation is given off in all directions but most of it is in the case of x rays or telecurie sources shut off by diaphragms so that it never reaches the body and in the case of surface radioactivity simply allowed to pass off into the surrounding air In interstitial irradiation all the energy from the source reaches the tissues (2) In external irradiation even the useful beam must in general pass through skin and normal structures before it reaches the tumor volume The amount that may be administered is limited by skin tolerance and this amount is in turn diminished by absorption in the first tissue that it traverses

It is evident that if interstitial irradiation could be administered simply and uniformly it would be the method of choice Unfortunately, it is often impracticable and reliance must be placed on the external method

This brief summary of some of the phenomena of radiation has not repeated all the subject matter which can readily be found in the references cited Definitions of basic terms descriptions of generators tubes radioactivity measurements of quantity and quality dosage in x ray and radioactivity and protection data are amply treated in these texts and already well known to radiologists

However an outline of the practical application of some physics and engineering technics instruments and calculations to the actual use of x ray radium and radio isotopes in daily practice should be of interest

X RAY

Application

BEAM DIRECTION

To affect the tumor the radiation must reach it and the whole tumor bearing volume The disease must first be located To aid the clinician there are ordinary radiographs those with an external marking system or those taken with the treatment machine setup itself Casts or shells of various plastics or plaster of Paris especially for the head and neck and the chest carry marks for the placement of the entrance and sometimes for the exit beams and aid the accuracy of day to day setup

The various field sizes may be obtained by cones or movable shutter diaphragms some with light beam indicators Several ingenious devices such as the pin and arc protractor and the axial beam director fix the angle of the beam with respect to the body while the back pointer gives the position and direction of the emergent ray as well

Trunk and head bridges or jigs allow the building up of the given part of the body into a known fixed shape by means of powder or water phantom material and aid the placing of the ports on this built up outline These bolus or bagging materials have nearly the same density and atomic number as tissue and are used to bring uneven body surfaces to geometric shapes so that the scatter may be brought to a known amount or the usual isodose curves used In the case of tangential or glancing fields as in breast treatment this is especially necessary as the distribution of dose throughout the whole volume would be most uneven if not unknown

SPECIAL TECHNICS

Included here are somewhat unusual methods of applying the x rays that may be applicable to a number of different parts of the body Rotation therapy may be either discontinuous which is an extension of the cross

firing technic to as many separate fields as possible or continuous, in which case the patient (or tube) can be pivoted during treatment about the tumor as the center of rotation The beam remains aimed at the tumor during the entire exposure and since the patient is turning the skin dose is spread out over the whole circumference

Grids, usually sheets of lead rubber with a checkerboard array of spacings have come into prominence lately as a means for increasing the tolerance of the skin by protecting alternate islands of it with the result that larger tumor doses can be given

Contiguous fields at nearly right angles could often be used in parts of the body of small curvature such as head and neck axilla etc, except for the high dosage regions of the overlapping beams at the adjoining edges Wedge filters used near the surface, are designed to cut down any hot spots" and produce a more even distribution throughout the tumor

Shielding of particular structures or surgical incisions is simple enough throughout the high voltage range if it is remembered that any lead must be covered with a material of low atomic number to absorb the soft secondary radiation Eye shields for instance may be wax dipped In the supervoltage range the necessary thickness of lead would make it too heavy and too bulky to place directly on the patient Here a combination of a holder at a distance plus a light beam to locate the shadow of the lead over the part to be protected will be sufficient in most cases

HIGHER ENERGY RADIATION EQUIPMENT

In recent years 2 mv x ray machines, of the resonance transformer and of the electro static generator type have come into use Since the development of radar technics powerful ultra high frequency oscillators have been used to accelerate electrons along a tube in the linear accelerator Some 4 mev units are being used for x ray therapy at present

The betatron uses an alternating magnetic field to accelerate electrons in a circular orbit and may be used to produce electron or x ray beams to perhaps 50 mev with reasonable therapeutic intensity A practical working model in this country operates at about 22 mev The medical use of the betatron is described in another chapter

The synchrotron has an accelerating device energized by a radio frequency field as part of its circular path These two devices are perhaps the best methods for obtaining electron energies of from 20 mev up to about 100 mev X ray intensities useful in medical work are available and the machines are fairly compact and reliable

In the cyclotron, relatively heavy positively charged particles are accelerated by an electrical field while being kept in a spiral path by a magnetic field Protons and alpha particles of nearly 400 mev and deuterons of nearly 200 mev can be obtained by different types of cyclotrons A main use of the cyclotron has been the production of radioactive isotopes

Neutron beams have been used in therapy to some extent and can be produced in an atomic pile or by using as target in the cyclotron a material the disintegration of which yields neutrons

Higher energy accelerators such as the synchro cyclotron, proton synchrotron bevatron, or cosmotron are in use at hundreds of mev and even designed for billions of electron volts for research purposes at present

Dosage Measurements

INSTRUMENTS

The thimble ionization chamber, so called because of its usual size and shape is the main part of most measuring devices To read in roentgens they must of course be calibrated against a standard chamber and one of the important considerations of any chamber is its constancy of factor with changing quality of radiation

Dosage rate or r per unit time circuits may be electronic units employing amplification or null systems in which a known current can be produced to balance that from the ionization chamber

Integrating circuits give total roentgens over a given time Some of these are used with monitor chambers that may not read roentgens but show the constancy of output of the tube

The thimble chamber itself separated from any circuit may be used as a condenser in

which case its loss of charge as measured by an accompanying electrometer can be calibrated This again is an integrating device

For use in routine calibration of x ray machines any of the above instruments should be portable and as small as possible To determine the dose distribution where there are abrupt changes such as at the edges of fields the ionization chambers should be small In such regions the output is also low and so more sensitive circuits are needed Crystals that emit visible scintillations when irradiated are very sensitive but their use especially at the lower voltages must be guided by their quality dependence In investigative work the above circuits are usually laboratory built and thus about as numerous as the number of institutions enjoying physics departments

MATERIALS AND METHODS

To determine dosage distribution for the different qualities field sizes and shapes distances thicknesses of body cone or diaphragm arrangements angles of incidence to the surface etc, the above instruments are used with a phantom material of the same density and atomic number as tissue Water is useful especially since the chamber can move continuously through it Pressdwood or wax usable for the higher voltages can be cut to the size and shape of the part of the body being studied and spaces can be cut out for the insertion of the ionization chamber

Much more information would be obtained by knowing the location of the surfaces of a given percentage depth dose value throughout the volume of each field than by having the center line depth doses only However three dimensional setups are difficult to work with and so the isodoses are usually plotted for two perpendicular planes each including the central axis of the x ray beam

Some automatic plotting devices have been designed in which the measuring chamber follows a given dosage value and the resultant isodose line is simultaneously plotted by a pen that follows the movements of the chamber

Over a few million volts where there is little change of emulsion blackening with quality films can be used to map the radiation They are usually sandwiched between slabs of Pressdwood and placed so that their plane includes the axis of the beam

Dosage Calculations

Before treatment starts the physical setup is planned on the basis of the position and extent of the region that is to receive a given dose Every problem is of course three dimensional

A nearly transverse section through the tumor center is usually taken using a flexible lead strip or other means This is drawn on transparent film and if this plane is also that of the central planes of the x ray ports the isodoses can be superimposed on the film and the resultant distribution mapped in A more complicated arrangement is that in which the various ports are not coplanar Here a mockup cast of a section of the body can be made a tumor region placed in it a plane through the latter selected and the external location and angle of possible ports to this added Then contour plotters or contour projectors will give the dosage distribution at an angle to the central axis of the x ray beam Other instruments simulate the position of the x ray machine with respect to the patient but instead of the port itself carry its corresponding isodose chart and the roentgens can be found at any point on or beneath the skin surface

An important parameter in judging the total effect on the patient is the volume or integral dose This can be obtained by multiplying the roentgens per gram by the number of grams and summing up for the whole volume of tissue irradiated Formulas and tables must be available for the different conditions of treatment

If the field is an odd shape the usual isodoses for rectangle circles etc will not hold There is a method in the literature for calculating odd shapes by dividing the field into small sections and adding the contributions of each Available isodose and center line depth dose charts can be found in the accompanying references and many data can be obtained from the Hospital Physicists Association of England

RADIOACTIVE ELEMENTS

Application

This section includes the use of radium radon and some radioisotopes whose suitability depends on their type of radiation

energy, half life and any biologic effect. Many of the radioisotopes made by neutron bombardment in the chain reacting pile or as a result of the fission reaction of uranium or produced in the cyclotron have been found useful as radiotherapeutic agents. These usable elements are mainly beta or gamma plus beta emitters of various energies and half lives. They are not only substitutes for radium and radon but some are preferable owing to the biologic problems encountered and others are an improvement owing to ease of handling or protection considerations. Table 13.1 lists the energies of the gamma and beta rays and the half lives of some of the elements that will be discussed below. If it is desired to utilize the gamma rays only, sufficient filter must be employed to absorb the beta.

TABLE 13.1—ENERGIES OF GAMMA AND BETA RAYS AND HALF LIVES OF CERTAIN ELEMENTS

Element	*Mass number*	*Mev Energy* *Gamma*	*Beta maximum*	*Half life*	*I*
Bromine	82	0.55–1.3	0.2–0.45	34 hrs	15.5
Cesium	137	0.66	0.5 1.2	33 yrs	3.4
Cobalt	60	1.2 1.3	0.31	5.3 yrs	13.5
Gold	198	0.41	0.96	2.7 days	2.4
Iodine	131	0.80 0.37	0.6	8 days	2.3
Iridium	192	AV 0.40	0.59	74.4 days	2.7
Sodium	24	1.4 2.8	1.4	14.9 hrs	19
Tantalum	182	1.1 1.2	0.5	117 days	6.1
Phosphorus	32		1.7	14.3 days	
Strontium +Yttrium	90		0.5 2.2	21.6 yrs	

EXTERNAL

For the treatment of a superficial lesion, a plastic or dental compound mold or thin plaster of Paris cast may have radioactive tubes, needles or seeds in its surface or some flexible material such as felt with an adhesive surface may hold the sources over the area to be treated. Radium, radon or radioactive cobalt alloy tubes, gold, tantalum or iridium rods or wires are all usable. Sandwich molds will cross fire such sites as the lip or outer ear. Plaques are small containers of various shapes and sizes that hold tubes for treating surface tumors. It is also possible to make up an odd shaped surface area of inert material and then activate it, which eliminates the protection problem during assembly.

For surface treatment with beta radiation the radon glass bulb about 4 mm. in diameter is thin enough to allow the passage of the beta rays and has been used for many years. Radium D plus E applicators utilize the betas from the radium E and decay with the twenty two year half life of the radium D. Phosphorus can be incorporated in small plastic plaques and then irradiated in the pile. The fission product strontium with its daughter yttrium is obtainable bonded in a metal foil and makes a more permanent plaque than the short lived phosphorus.

Telecurie therapy units formerly containing radium but lately employing cobalt utilize the gamma rays and are set up in much the same manner as an x ray machine. A large protection head of lead or tungsten houses the source at target–skin distances equivalent to those in x ray therapy. Another possibility, because of its relatively high energy and long half life, is cesium if it can be concentrated into a small enough volume.

INTRACAVITARY

These sources are usually linear, such as tubes in tandem in various holders or applicators, some of which may employ partial shielding. The tubes are usually radium or

radon but may also be obtained in the form of cobalt with a suitable filter such as stainless steel Small area distributions as in a vaginal wall applicator may be used in some cases Concerning cancer of the cervix an equation can be set up in which the variety of applicators for treatment equals the number of departments using radioactive materials for this purpose Most systems such as the Stockholm Paris Manchester and their variations try to space the separate tubes to give an adequate dose two or more centimeters lateral to the cervical canal or to the paracervical triangle Methods of insertion also vary flexibility of placement vying with maintenance of positioning

Solutions of sodium bromine or cobalt in rubber bags will treat the surface of the bladder fairly uniformly Or colloidal gold may be used with no container and would envelop and treat from all sides any parts of the tumor projecting from the bladder wall

Colloidal gold has been effectively injected into the pleural cavity to treat effusion and into the abdomen for ascites Chromic phosphate has also been of aid for pleural effusion

INTERSTITIAL

Radium or cobalt needles or tantalum wire from one to several centimeters long may be put throughout the tumor mass itself Small gold cobalt titanium or iridium sources in flexible nylon ribbon can be sewed through the tissue All the above are withdrawn after the specified dose is delivered

For permanent implants radioactive gold grains covered with stable gold or platinum may be used instead of the usual radon seeds Special injector guns have been devised to inject several of the grains without withdrawal although some prefer the multiple trochar needle porcupine method that gives a picture of the implant as a whole The 2 7 day half life of the gold compares with that of 3 8 days for the radon

Colloidal gold is apparently nontoxic and remains fairly well localized within the tissues in which it has been injected such as the prostate or in the parametrium for carcinoma of the cervix

The selective physiologic uptake of iodine by functioning thyroid tissue results in the interstitial deposition of radioactive iodine within some carcinomas of the thyroid and their metastasis The radioactive material in these cases can be given orally

Whole body radiation might perhaps be considered under the interstitial heading as in the intravenous injection of radiophosphorous for polycythemia vera

Dosage Measurements

INSTRUMENTS

The question of proper measurement of dosage due to radioactive elements is much more difficult than the corresponding one for roentgen rays There are only small amounts of the radioactive material used for most cases and the distances from the sources at which the dose is wanted are in general so small that the size of the ionization chamber makes a large difference

For most work the ionization chambers must be tiny and the measuring circuit very sensitive Otherwise the instruments are similar to those used for x ray work and again may be of the roentgen per minute or total roentgen type

The extrapolation chamber is particularly applicable for the measurement of beta ray plaques and for the depth doses in the first few millimeters of tissue for which other chambers are too large

Films can be used at the higher gamma energies because of the lack of appreciable quality effect

Small ionization chambers or scintillation crystals at the end of long small diameter probes measure the rectal and bladder dose when cervix applicators are being used This is usually done at the time of insertion so that if there is any danger of overdosage to the rectal wall for instance the parts of the applicator could be rearranged

An automatic isodosimeter has been built that employs a small scintillation crystal and amplifier and will trace on a sheet of paper the lines of equal dosage rate around a given configuration of radioactive material Specially designed molds can be checked before use or reconstructions of some interstitial implants can be made in time to alter them if necessary before treatment ends

External scanning is often carried out on patients who have had isotopes such as gold or iodine internally administered A scintiscanner employs a collimated crystal detector and moves automatically across the surface of the patient s body while simultaneously marking on a chart the points of greatest radiation In this way a picture is drawn of the distribution of radiation within the body

Dosage Calculations

Most gamma ray dosage calculations are based on the value of the roentgen per millicurie hour at 1 cm from a point source called the I_γ Owing to the different spectra and energies of the isotopes, these values are different That for radium or radon is 8 4 r per mg or mchr at 1 cm whereas the value for gold is 2 4 If the geometry of the radioactive distribution is known, the problem of dosage usually yields to the ordinary calculus

EXTERNAL

Teleradioactive units utilize isodose curves in the same manner as x ray beams although the penumbra is liable to be larger owing to the greater size of the source as compared to the focal spot of an x ray tube

Isodoses under an applicator with a flat or curved area depend on the distribution of the radioactive material The center line doses for various sizes shapes and distances from radium configurations are given by Quimby and by Paterson and Parker within the references for this chapter

For distances greater than a half centimeter these same tables can be used for other gamma isotopes if the number of milligram hours per 1 000 r is multiplied by the ratio of the radium I_γ to the radioisotope I_γ For instance if cobalt were being used instead of radium the milligram hours would be decreased to 8 4/13 5 or 0 62 to give the number of roentgens as specified for radium Further corrections would have to be made for absorption if the filters were different

INTRACAVITARY

When the arrangement is linear one or more tubes in tandem the dose is readily found from charts prepared by the above authors If the element is not radium the I_γ correction can again be made

If the arrangement is a fixed one, isodoses can be plotted before treatment If the sources are movable with respect to each other such as in many cervix treatments radiographs are taken from which a three dimensional reconstruction of the implant can be made or the correct calculations applied to obtain the dose at specified points

For a solution in a body cavity such as the bladder both the gamma and the beta ray dose to the wall have to be considered For given geometric shapes such as a sphere formulas are given in the textbook references of this chapter which will allow the calculation of these doses in roentgens or rads

INTERSTITIAL

If the seeds or needles are distributed throughout a tumor mass according to the rules of Paterson and Parker or of Quimby their charts and tables are then followed for the assessment of dose As has been pointed out in the recent literature if the element is not radium the I_γ correction alone would not be true very close to the source when the filters were different If one filter were thicker the dose close to it would be relatively lower as the obliquity of filtration would be greater

For permanent implants the different half lives have to be considered If all the factors are the same except for the I_γ and the half life then the number of millicuries of the isotope to give the same number of roentgens as the radon would be obtained by multiplying the necessary millicuries of radon by approximately 3 8/Half Life of Isotope x 8 4/I_γ of Isotope

The above is an illustration of one of the more simple equations to adapt existing tables for radium to the radio elements If the over all treatment time is very different with another isotope then even though the same dose in roentgens is given as with radon a different biologic effect would be expected

If the isotope is distributed throughout a tumor mass then there is no filter and the beta radiation is present If the size of the mass is greater than the beta particle range the calculation is straightforward in that the energy absorbed is equal to the energy emitted The

effective half life which is a combination of the physical half life and the rate of biologic elimination from the mass must be used If the shape is one for which the calculus has a ready formula then the gamma ray dose is obtainable from published tables For shapes that are prevalent biologically but odd to the mathematician each problem must be solved by him separately

A radiographic check of an opaque implant is excellent to determine if there are any hot spots resulting from the grouping of the sources or if the distribution differs too widely from the attempted one There are several radiographic methods of computing the dose in the latter case

The extent of that part of radiologic physics applied to radiation therapy has been increasing greatly in the last decade especially with the advent of higher and higher voltage x ray equipment the increasing use of radioactive isotopes and the problems of protection of personnel and patient associated with each of these Adequate information to gain any working skill in the subject would require at least a whole book and such texts are already available The present chapter therefore has attempted to outline the field as applied to therapy alone and to summarize a general description of the physics mathematics and engineering gadgetry necessary in the physical basis of radiation therapy

CHAPTER 14

The Radiosensitivity of Tumors

George K Higgins

INTRODUCTION

The effects of the different ionizing radiations used in the treatment of tumors differ quantitatively rather than qualitatively, and the actual fundamental tissue responses to each are similar (Some qualitative differences have been suggested in protozoa but do not appear significant for this study) [23]

In order for radiations to be effective the energy must actually be absorbed by the tissues and not merely pass through them (Grotthus Draper Law) This absorption results in the ionization of the molecules of the tissue cells or surrounding medium and initiates a chain of chemical reactions not yet identified During the earlier reactions in this series of chemical changes no evident biologic effects can be determined This so called latent period may extend from minutes to years

The functional changes that occur after the latent period are many and varied They may result in mutation of a gene the breaking of a chromosome increased permeability of a membrane inhibition or destruction of a neoplasm death of an animal or any one of many radiobiological phenomena [30]

MORPHOLOGIC EFFECTS OF IRRADIATION UPON CELLS AND STROMA

Differences in Response Between Cancer Cells and Normal Cells

It is well substantiated that during rapid growth the cell becomes more predisposed to injury by the radiant energy than cells at rest It seems that damage to the enzyme systems and chromatin structures play the important roles Unfortunately the clinical response of a tumor subjected to ionizing radiations can not be predicted by the activity of these biologic processes [12]

Undifferentiated tumor cells are the most radiosensitive probably because of a greater metabolic activity Cells in the active stages of mitosis, especially during the prophase are five to ten times as susceptible to ionizing radiations as comparable cells in the resting state, partly because of their increased metabolic activity and partly because of the greater surface area of chromatin exposed to the injurious rays Furthermore, those cells of a specific tumor type having the most hyperchromatic nuclei absorb the most and are the most susceptible to ionizing radiations

Morphologic Cellular Changes Resulting from Irradiation

There is no single morphologic change peculiar to irradiation There is an increase in the size of the cell partially from absorption of water [3] Sometimes as is seen prominently in vaginal smears some irradiated cells assume massive proportions owing to an actual increase in the amount of protoplasm If the damage is severe these changes are followed by the development of vacuoles [21] (hydropic degeneration), or the accumulation of fat droplets in the cytoplasm (fatty degeneration) Still greater damage results in the death of the cell with the formation of coagulation necrosis and finally in dissolution of the cell (liquefaction necrosis)

EFFECTS OF IRRADIATION UPON THE CYTOPLASMIC STRUCTURES

The Golgi apparatus of carcinoma cells obtained from rats when exposed to ionizing radiations changes the original netlike arrangement to an indefinite mass then to dis

Fig 14 1 Epidermoid carcinoma of the cervix Cell swelling and squamous degeneration with still relatively intact basal layer (Courtesy Dr Fred W Stewart and Dr Joseph H Farrow)

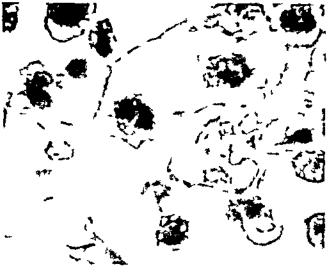


Fig 14 2 Marked hydropic degeneration in melanoma cells after radiation

crete small masses that finally rearrange themselves to form the netlike structures again—the entire process occupying about 18 hours from the time of irradiation [9] Changes in the mitochondria likewise occur rapidly after irradiation and appear to return to normal after a period of hours or days [28] The number of centrioles increases up to 72 hours after exposure but then slowly decreases again It could not be determined whether this alteration resulted from fragmentation of the centrioles or from inhibition of cytoplasmic division without a similar inhibition of the centrioles [10]

EFFECTS OF IRRADIATION UPON THE NUCLEUS

The nucleus is more prone to injury than the cytoplasm because it absorbs more radiant energy—a property retained by even the simpler compounds of nucleic acid Also in contrast to cytoplasmic reaction to injury, evident morphologic alterations within the nucleus do not occur until severe functional damage has been sustained Therefore the effects of small and moderate exposures are evident not by alterations of chromatin etc but chiefly by an inhibition of mitosis With less damage cell division is soon re-established More effective doses prolong the period of inhibition and some cells both tumor and normal may live for months or years without the power to reproduce The part of the reproductive mechanism injured is not known

Even after considerable irradiation certain cells retain or recover the power to reproduce often in an altered form In some instances this results in the death of the cell especially at the time of mitosis or in the progeny after division Other daughter cells assume bizarre forms or develop into giant cells

Greater damage to the irradiated cell may result in the production of intranuclear [17 26] as well as intracytoplasmic vacuoles and irregularities of the chromatin When the tolerance of the nucleus is approached it becomes shrunken and often peculiar appearing With death of the cell the usual changes of coagulation necrosis are followed by pyknosis karyorrhexis and karyolysis and eventually complete liquefaction

MATURATION FOLLOWING RADIATION TREATMENT

Under the influence of irradiation—probably from the destruction of the less differentiated tumor cells rather than any intrinsic change—tumor cells undergo changes that suggest maturation This is most evident in squamous-cell carcinomas by the addition of prickle-cell formation and cornification and in basal cell carcinomas by comparable changes Some basal cell carcinomas also appear to form glands [1] There is less evidence that glandular carcinomas form glands (mucus production may follow any irritant) and probably none that sarcomas mature to form collagen bone etc, under such influence

SPINDLING

Elongation or spindling of cells such as is evident in certain squamous cell and glandular carcinomas decreases their response to irradiation probably from a decreased exposable area Since other tumors with similarly shaped cells such as fibrosarcoma leiomyosarcoma, and malignant neurilemmoma are relatively resistant to irradiation the form of the cell may be a significant factor

RADIORESISTANCE

Radioresistance develops in part from the destruction of the more radiosensitive cells and the persistence and regeneration of the more resistant ones A later return to a radiosensitive state is due to a new generation of cells that are again radiosensitive The radioresistance that most tumors ultimately develop may be due in part to the great predominance of those radioresistant cells but much of it is the result of decreased blood supply and increased fibrosis

Effects of Irradiation upon the Supporting Tissues

It is probable that much destruction of tumor cells is accomplished by the body defenses following irradiation as well as by the lethal effects of ionizing radiations directly upon the tumor cells Examples of this consist of the greater exposures (sometimes ten to fifteen times) necessary to destroy cancer cells in vitro as compared with those necessary to destroy similar cells in vivo and the persistence of viable malignant tumor cells months

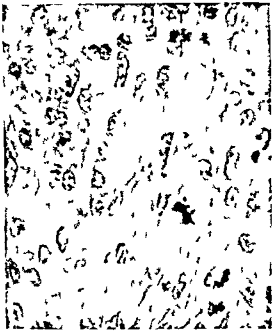


Fig 14 3 Atypical mitoses following irradiation Death of cells during mitosis and in the daughter cells is evident

Fig 14-4 Atypical mitoses following irradiation High power magnification of photomicrograph shown in Figure 14 3

Fig 14 5 Atypical mitoses following irradiation High power magnification of photomicrograph shown in Figure 14-3 demonstrating bizarre forms of mitotic division

Fig 14-6 Atypical mitoses following irradiation High power magnification of photomicrograph shown in Figure 14 3 demonstrating atypical mitoses in a dying cell

after cessation of radiation therapy in tumors that eventually become sterile [13]

Neoplasms with damaged stroma respond poorly to irradiation Likewise a tumor bed

Fig 14 7 Carcinoma of the cervix removed three months after intensive irradiation Although the cells still appear viable the tumor has not recurred in four years

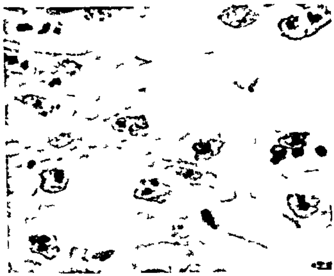


Fig 14-8 Carcinoma of the cervix Higher magnification of photomicrograph shown in Figure 14 7 demonstrating viable tumor cells

of cartilage or bone is not conducive to satis factory results from radiation therapy How ever a tumor bed of highly vascularized healthy connective tissue or a thick layer of striated muscle usually shows the greatest therapeutic response

THE NATURE OF TISSUE REACTION TO IRRADIATION

The inflammatory reaction induced by ion izing radiations differs in no fundamental manner from that produced by other injurious agents The process tends to be slower es pecially if smaller doses of irradiation are administered It usually takes some days for the clinical appearance of the reaction if one or more erythema doses are delivered to the

area with the maximum intensity developing still later Dilation of the vessels occurs An abundant serous exudate causes a widening of tissue spaces and a subsequent deposition of fibrin occurs It has been shown by Saphir [20] in pulmonary metastases that fibrin surrounds the tumor cells preventing their growth eventually causing their atrophy and finally their complete destruction, it appears probable that the fibrin formed during the inflammatory reaction of irradiation acts similarly

The margination and emigration of the neutrophils occur simultaneously with the formation of the serous exudate but usually mononucleated cells are more prominent until there are definite areas of necrosis With the repair come eventual fibrosis and decreased vascularity chiefly the result of the irradiation of the connective tissue and vessels comprising the tumor bed

EFFECTS OF IRRADIATION UPON CONNECTIVE TISSUE

Collagen is more sensitive to irradiation than resting fibrocytes but less so than the active fibroblasts The response of collagenous fibers to small exposures of irradiation is revealed by thickening and by decreased staining properties About 1300 to 1500 r produce definite changes including necrosis Larger doses produce still more injury indicated by fibrillation segmentation loss of fiber outlines and a failure to stain by the usual methods [27] Eventually there is liquefaction of the fibers In healing fibroblasts (some of which develop from the polyblasts or wander in from the adjacent regions) form new collagenous fibers that usually are coarse and abundant Eventually the contraction of these fibers compresses the vessels and results in a dense avascular scar that tends to render the tumor radioresistant This fact is important for obviously the injudicious use of radiation therapy may produce so much fibrosis before destruction of the neoplastic cells has occurred that a radiocurable tumor is transformed into one that is radioresistant

Radiation injury to the fibrocytes is manifest The cytoplasm becomes increased and basophilic and the cells assume a polygonal or fusiform shape with tapering ends The nucleus and nucleolus both become enlarged but retain their original shapes The chromatin becomes coarser More marked changes become evident with increased and repeated exposure

Fig 14 9 Radiation fibroblasts (X 1000)

THE EFFECTS OF IRRADIATION UPON THE VASCULAR BED

The earliest change is a dilation of the vessel wall With small exposures the condition is *temporary* and no permanent changes can be detected Larger exposures (500 r or more with medium voltage x rays) result in permanent dilation with resulting telangiectases The larger doses used in treating tumors result in swelling and diffuse or focal proliferation of the endothelial cells which narrows the lumen and may completely occlude it Exposures of 1200 r produce vacuolization and necrosis of the endothelial cells—damage severe enough to result in thrombosis [27]

The elastic tissue disintegrates and is replaced by collagen this change is helpful in differentiating radiation effects on the vessels from other vascular diseases The muscle cells become swollen and vacuolated then hyalinized and gradually replaced by collagenous fibers Radiation fibroblasts become evident In the outer coats undifferentiated cells of the adventitia disappear The total diameter of the

vessel wall is increased, chiefly at the expense of the lumen [27] The narrowing together with thrombosis from endothelial damage may interfere considerably with the blood flow through the tumor, producing ischemia or infarction resulting in destruction of considerable tumor cells This necrosis from vascular occlusion is a factor responsible for the favorable temporary response of some radioresistant tumors

CLINICAL CONSIDERATIONS OF TUMOR RADIOSENSITIVITY

Radiocurability must be differentiated from radiosensitivity Radiosensitive tumors are those that show the most regression or degeneration from the least exposure to irradiation Warren [28] has advocated the use of the term radiosensitivity' to indicate a significant tissue response to less than 2 500 r administered in the ordinary therapeutic manner radioresponsiveness to a response from irradiations measuring between 2 500 and 5 000 r and 'radioresistance to response produced only after still larger exposures

Desjardins [7] has tabulated the sensitivity of the various tissue cells to ionizing radiations He found the leukocytes especially the lymphocytes neutrophils and eosinophils to be the most sensitive cells in the body Next in order were the mucus producing cells of the basal epithelium such as the salivary epithelium the bronchial lining cells and the mucus producing cells of the gastrointestinal tract The basal epithelium of the testicular tubules and the epithelium of the ovary followed Fibroblasts were fairly sensitive Fibrocytes were rather resistant but even more so in the order mentioned were cartilage bone muscle and fat cells Nerve cells were the most resistant In general this order of sensitivity correlates well with the life expectancy of the cell those that have the shortest life expectancy are the most radiosensitive while those with the greatest life span are the most radioresistant

He also found that these relative responses of the various normal tissues were retained by the tumors derived from them

It is significant however that even the most radiosensitive tumors contain some rather resistant cells Thus in treating these tumors several thousand roentgens may be necessary as a sterilizing dose even though only several hundred are needed to give clinical regression because of the destruction of the majority of the cells

RADIORESPONSE OF TUMORS

The Response of Tumor Types to Irradiation

CARCINOMAS

The radiosensitive undifferentiated transitional cell carcinoma of the nasopharynx which literally 'melts after several hundred roentgens in divided doses can be contrasted with the well-differentiated squamous cell carcinoma that requires from 3,000 to 6 000 r for significant effects However because all types of carcinoma contain some radioresistant cells the sterilizing dose for all should consist of from 3 000 to 6 000 r

Squamous cell carcinomas occurring on the skin surface usually show a more satisfactory response than do those of comparable structures arising on the mucous surfaces Basal cell carcinomas usually are more easily destroyed than squamous cell carcinomas

A few glandular carcinomas are unusually radiosensitive e g , seminomas of the *testis* but unfortunately those tumors most frequently encountered—carcinomas of the stomach colon etc —are rarely if ever curable by radiotherapy In general glandular carcinomas do not lend themselves to therapy as well as epidermoid carcinomas

SARCOMAS OF THE SOMATIC TISSUES

Sarcomas should be considered radioresistant although examples are encountered which exhibit a considerable response such as the *liposarcomas* where 5 year cure rates can be obtained [19] This is unusual since fatty tissue is relatively radioresistant

Osteogenic sarcomas usually react poorly to radiotherapeutic efforts

Synovial sarcomas vary in structure sufficiently to show more than the usual differences in radioresponse

Fibrosarcomas usually give slight and temporary response to irradiation Most *malignant neurilemmomas* respond in a similar but even less satisfactory manner *Neuroblastomas* are

radiosensitive whereas *ganglioneuromas* are resistant to irradiation

Radiation induced alterations are least evident in *chondrosarcomas* which almost never give more than fleeting response The *myxosarcoma* not mixed with other related tumor elements is rare and insufficient data are available for conclusions but it appears to respond unsatisfactorily

TUMORS OF LYMPHOID AND HEMATOPOIETIC TISSUES

Response of Normal Tissue to Ionizing Radiation

The lymphoid tissues are most sensitive The germinal centers are injured most severely, but the lymphocytes are also very sensitive The reticulum cells in the sinusoids are less severely damaged and with proper exposures they may be found apparently intact when the parenchyma appears to have disappeared Recovery with replacement lymphocytes is rapid unless sterilizing doses have been applied The changes in the lymphocytes consist of cellular enlargement clumping of the chromatin vacuolization of both nucleus and cytoplasm and some instances of nuclear pyknosis [11] When regeneration occurs peculiar appearing cell types are common including bizarre forms giant cells and cells in atypical mitoses

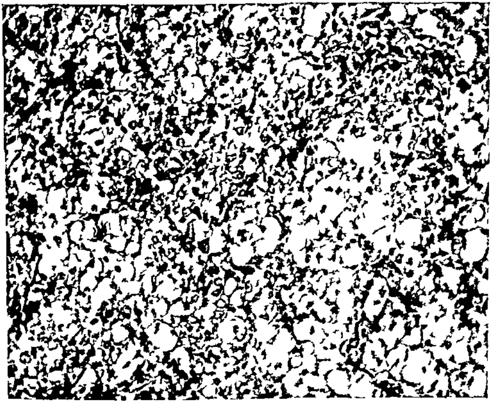


Fig 14 10 Radiosensitive lipsarcoma (Courtesy Dr Fred W Stewart and Dr Joseph H Farrow)

The somatic sarcomas in infants and young children frequently react dramatically although temporarily to irradiation [19] It is not unusual for a large fibrosarcoma to disappear from exposure of 800 to 1 000 r over a period of 4 to 5 weeks Such response should not be construed to indicate curability since consistently many of the neoplastic cells remain in full vigor Such reduction in size however may be of value in making surgical removal possible or more readily accomplished

The benign counterparts of the tumors discussed are radioresistant

Destruction of the marrow cells in irradiated areas is evident within two days after exposure and may be almost complete a few days later except for the reticuloendothelial cells These latter form the foci for regeneration of the mononucleated cells, the granulocytes, and finally the erythropoietic series Hemopoietic tissue appears to be more severely damaged and recovers later than lymphoid tissue [11]

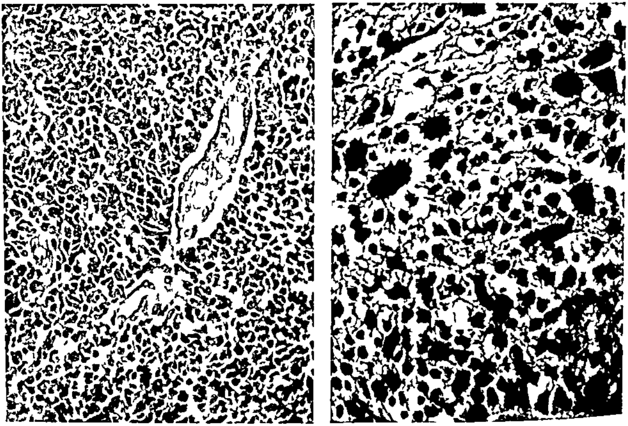


Fig 14 11 Variable radiosensitivity of tumors of the peripheral nervous system (*Left*) Neuroblastoma The poorly differentiated tumor cells are radiosensitive and are usually destroyed by moderate doses of irradiation Even the metastases may be destroyed by radiation therapy (*Right*) Ganglioneuroma Showing tumor cells of mature character which are radioresistant Surgical removal is the indicated therapeutic procedure

Lymphomas Hodgkin s Disease and Leukemia

Tumors and related diseases of lymphoid tissue are among the most radiosensitive of all neoplasms—50 to 100 r daily for a total dose of 300 to 400 r is usually sufficient to cause clinical disappearance of most early growths However with such small exposures recurrences are usual In only about 50 per cent of the cases will 1 500 to 2 000 r delivered to the tumor in the course of 10 days destroy the tumor, and frequently 3 000 to 4,000 r will be needed to sterilize a moderate sized neoplasm, in other words approximately ten times the palliative dose is required [15]

Tissue infiltrations respond in a manner similar to the primary disease in the lymph nodes Widespread radiation therapy to the leukemic patient also reduces the number of white cells in the bone marrow the infiltrated organ, and the circulating blood

RADIOSENSITIVITY OF EMBRYONAL TUMORS

As would be expected from the character of the cells embryonal tumors respond favorably to irradiation

Tumors composed of a single type of tumor cell e g , seminoma of the testis sympathicogonioma of the adrenal offer better prognoses than many other tumors that show comparable malignant characteristics Even

the metastases of some can be sterilized [24]

Tumors characterized by mixtures of cells e g Wilms s tumors usually contain tumor foci that are radioresistant and although the original response may be dramatic the eventual result is unfavorable

Radiosensitivity of Tumors According to Anatomic Location

RADIOSENSITIVITY OF TUMORS OF THE SKIN AND ITS APPENDAGES

Reaction of Normal Skin to Irradiation

The changes in the tissues incident to irradiation result from two reactions First the severity of the damage The radiosensitive upon the active cells of the hair follicles cause stoppage of hair growth either temporary or permanent Sweat and sebaceous glands are similarly affected Squamous metaplasia of the ducts of the sweat glands has been observed after irradiation [11]

The second reaction is inflammation followed by pigmentation atrophy and telangiectasis The increased pigmentation is believed to result from an increased tyrosine tyrosinase reaction in a manner similar to that induced by ultraviolet radiation [8]

The atrophy is manifested by a flattening of the rate pegs decreased thickness of the epidermal layer and decreased or absent appendages

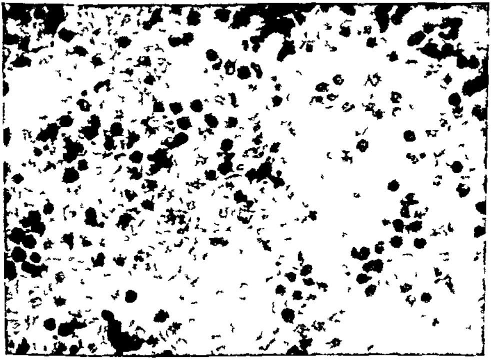


Fig 14 12 Lymphosarcoma Pyknosis and rapid cellular disintegration following radiation treatment The distribution of necrotic cells is irregular (Courtesy Dr Fred W Stewart and Dr Joseph H Farrow)

cells constituting the germinal layers of the epidermis and the proliferating portions of the dermal appendages fail to reproduce satisfactorily and undergo focal necrosis or show widespread destruction The more mature squamous cells are more radioresistant and suffer little or no significant injury If there is sufficient destruction of the basal cells over an area large enough so that they cannot regenerate or be replaced from the adjacent areas ulceration results Comparable effects

In the underlying dermis polyblasts may persist indefinitely The injured blood vessels undergo thrombosis and disappear except for the fibrous elements which become merged with the surrounding connective tissue occasional vessels compensate and become telangiectatic Unless the damage is considerable necrosis with subsequent hyalinization is not marked since the collagen tends to be more resistant to injury Because the damage results usually from the accumulation of numerous

exposures over a considerable time evidences of overexposure may not be evident for months or even years Both the protracted and the recurrent exposures produce the chronic radiodermatitis

The acute radiation reaction of the skin as of the deeper tissues is more intense when the individual exposure is greater while the late effects are more dependent upon the total dosage

Fig 14 13 Radiation atrophy of the skin (X 450)

Sensitivity of Skin Tumors to Irradiation

Papillomas Adenomas and Glandular Carcinomas The fibroepithelial papillomas are resistant Infectious papillomas including plantar warts give satisfactory response to surface irradiation unless they are deeply rooted infected or ulcerated Both adenomas and carcinomas of the various cutaneous glands respond poorly to the ionizing radiations

Basal and Squamous Cell Carcinomas The destruction of basal cell carcinomas by irradiation is due to several factors such as accessibility small size superficial growth lack of metastases and a tumor bed favorable to therapy

Because basal cell carcinomas offer most satisfactory conditions for repeated biopsy the roentgen changes incident to these tumors have been observed in detail Stewart and Farrow [25] found

Shortly after the beginning of treatment the exudative cells become separated by edema lymph stasis is evident in dilated lymphatics and small foci of fibrin appear in the stroma Within four or five days the first definite change appears in the tumor cells themselves This consists in the appearance of foci of squamous metaplasia These foci are sharply local so local in fact that although the matter cannot be proved one is forced to assume that they depend for their distribution upon undetected circulatory alterations in the tumor These areas of squamous metaplasia gradually become more numerous The acidophilic squamous cells become swollen and vacuolated and the end stage of the degenerative process seems to consist in a shrunken ring of acidophilic cytoplasm with a central collection of degenerated leukocytes This progressive degenerative metaplasia is not uniform in type In other areas the sheets of basal cells appear to be broken up by exudate and there results areas of elongated spindle cells which fray out into the stroma and which become separated from one another by exudate mucin and swollen degenerated elastic tissue The spindle cells gradually become acidophilic shrunken and infiltrated by leukocytes Throughout the process up to the end stages of degeneration there are apt to persist in the midst of granulation tissue islands of histologically unaltered tumor which cannot be distinguished

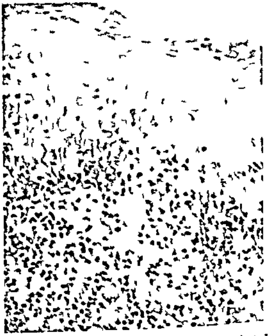


Fig 14 14 Inflammatory reaction still evident 18 months after Irradiation (X 100)

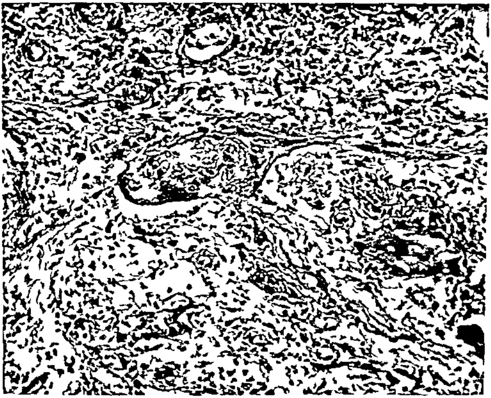


Fig 14 15 Regressing basal-cell epithelioma showing marked squamous metaplasia (Courtesy Dr Fred W Stewart and Dr Joseph H Farrow)

from the original lesion The stimulation of connective tissue in the sense of true fibrosis seems to play little or no part in the disappearance of the tumor since the latter is gone before any fibrosis begins to appear

In general the squamous cell carcinomas present the same reactions and the same problems as the basal cell group The minute ones may be destroyed by ionizing radiations Larger tumors which have infiltrated deeply and become infected respond less favorably Infiltration into tissue such as bone or cartilage (either basal or squamous cell tumor) militates against using irradiation to effect a cure

Although carcinomas frequently arise in multiple foci there is little indication that irradiation of the surrounding epidermis aids in preventing the subsequent development of other carcinomas in fact it may abet the formation of a new tumor

The squamous cell carcinomas of the vulva and anus differ from those elsewhere by their early metastases to regional lymph nodes and the moist poorly responsive tumor bed does not contribute to a favorable bioradiologic reaction

Pigmented Nevi and Malignant Melanomas Nevus cells are at least as resistant to irradiation as the adjacent tissues and irradiation appears to have no place in their treatment

Fig 14-16 Marked fibrosis in a metastatic melanoma removed three months after intensive irradiation (× 450)

In three instances known to the author in which pigmented nevi were irradiated 700 to 800 r given in five sessions, 100 kv with no filter, there gradually occurred some decrease in pigmentation after four years no untoward changes were evident

Only 3 or 4 per cent of *malignant melanomas* show any significant response to irradiation Several months after therapy most treated melanoma nodules show no marked change from comparable untreated ones in the same patient Fibrosis the most outstanding feature of the treated nodules becomes obscured as the melanomas increase in size

TUMORS OF BLOOD VESSELS

Capillary hemangiomas composed chiefly of endothelial cells and surrounding reticulum and collagenous fibers, assume various forms including the De Morgan spot and strawberry mark they are more sensitive to radiation therapy than the other tumors of blood vessels The endothelial cells are injured by relatively small exposures With swelling of the cytoplasm and the inflammatory exudate compressing the vessel wall, the lumen is narrowed and when necrosis develops the blood in the lumen clots The resulting thrombus becomes organized and eventually an avascular fibrous lesion results

Cavernous hemangiomas develop from the capillary type when the intravascular pressure dilates the capillary walls to form large sinuses and sacs Such changes reduce the radiosensitivity of these tumors because now the flattened endothelium forms only a narrow rim on the periphery of the sac Moreover the ionizing radiations must pass through larger vessels that help protect the more deeply situated cells

Hypertrophic hemangiomas or benign hemangioendotheliomas are radioresistant [18] Cirsoid hemangiomas or aneurysms are also radioresistant The corresponding lymphangiomas are more radioresistant than their hemangiomatous counterparts

The *angiosarcomas*—malignant hemangioendotheliomas and lymphangioendotheliomas—respond rather well at first to radiation therapy but such treatment is chiefly palliative

Kaposi s Hemorrhagic Sarcoma The earlier tumors are radiosensitive and will disappear under dosages of 1 000 to 2,000 r of unfiltered low voltage roentgen rays or corresponding exposures with a radium plaque The older tumors and especially the fibrosed ones are much less responsive to radiation therapy

TUMORS OF BONE AND CARTILAGE

Growing bone and cartilage are sensitive to the usual therapeutic exposures but adult cartilage is resistant The bone matrix is undoubtedly very resistant as is probably the osteocyte, but bone seldom can withstand more than moderate exposures without undergoing necrosis because of the vascular injury incurred Moreover, bone and cartilage form a poor bed for the radioresponse of tumors infiltrating these structures

Ewing s tumor, reticulum cell sarcoma and myeloma are radiosensitive tumors and undoubtedly could be cured if distant metastases did not occur

Giant cell tumors are usually curable by either surgical resection or radiotherapy The malignant forms however are comparable to sarcomas of the supporting tissues and are radioresistant as are chondrosarcomas and (from a practical point of view) osteogenic sarcomas

TUMOR OF MUSCLE

Muscle is a radioresistant tissue and does not show significant injury from therapeutic exposures of roentgen rays Excessive exposures from intracavitary radium does at times result in injury to adjacent muscle [22] Leiomyosarcomas and myoblastomas are radioresistant

RADIOSENSITIVITY OF THE EYE AND TUMORS ORIGINATING IN THE EYE

The conjunctiva and cornea are not injured more than other delicate squamous surfaces and withstand considerably greater exposures than the lens This appears to be true also of the iris choroid and retina as well as the sclera

The changes in the lens usually result over a period of months to years The injury is manifested first in the posterior pole just beneath the capsule as minute ground glass

translucencies that gradually increase in size and opaqueness until they form circumscribed disc shaped areas There is slow but usually progressive cataract development [6]

For hemangiomas on the surface of the sclera (or cornea) or adjacent structures beta irradiation is satisfactory (Beta rays are obtained from radium D or radioactive stron

to fall into two distinct groups (1) the well differentiated radioresistant tumors which tend to cornify and (2) the poorly differentiated radiosensitive tumors including transitional and lymphoepitheliomatous types

Carcinomas of the Pharynx and Larynx Although the degree of differentiation varies most carcinomas arising in the nasopharynx

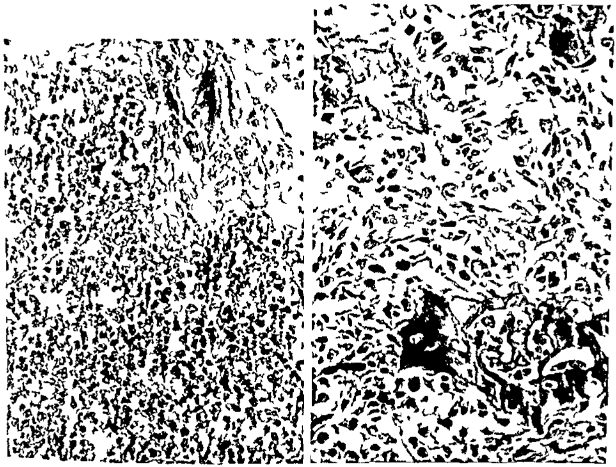


Fig 14 17 Variable radiosensitivity of malignant bone tumors (*Left*) Ewing s endotheliosarcoma of bone usually very radiosensitive but difficult to sterilize completely by irradiation (*Right*) Osteogenic sarcoma moderately sclerotic with formation of bone spicules A radioresistant bone tumor

tium filtered to remove other rays) Of the two common tumors of the eye the malignant melanoma is radioresistant and the retinoblastoma unless very small responds only after the global structures are so damaged that blindness results

RADIOSENSITIVITY OF TUMORS OF THE UPPER RESPIRATORY AND DIGESTIVE TRACTS

The epidermoid carcinomas arising from the mucous linings of the head and neck tend

the tonsillar region the hypopharynx the piriform sinus arytenoepiglottic fold etc are undifferentiated and radiosensitive The results vary considerably in different locations those in the tonsillar regions the nasopharynx and the aryepiglottic regions offer better prognoses while those in the piriform sinus are seldom sterilized In some the tumors are sufficiently radiosensitive to obtain sterilization in the lymph nodes as well Carcinomas of the epiglottis vocal cords and postcricoid regions are usually more differentiated and

although only moderately radiosensitive cures of the tumors in these locations can be obtained by irradiation

Carcinoma of the Lip Although carcinoma of the lip is usually a well differentiated squamous cell carcinoma and not very radioresponsive its accessibility permits excellent results by irradiation

Carcinoma of the Mouth The anterior oral carcinomas tend to be differentiated Those arising on the buccal surfaces and floor of the mouth are somewhat less so than those on the gums and hard palate

The tumors of the dental anlagen vary greatly in the types of tissue composing them and in the degree of their malignancy In most however because of their radioresistant components their proximity to bone and their inaccessibility the treatment by irradiation is unsatisfactory

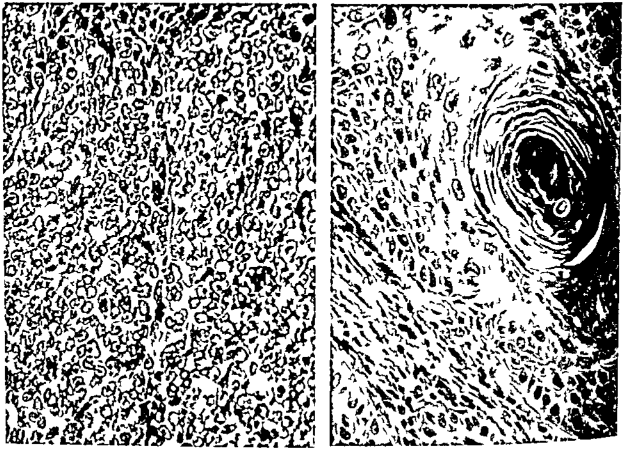


Fig 14 18 Variable radiosensitivity of pharyngolaryngeal cancers (*Left*) Radiosensitive noncornifying undifferentiated epidermoid carcinoma with transitional-cell features from the pharyngeal wall This cancer responded well to irradiation and has not recurred after three years (*Right*) Well-differentiated squamous-cell carcinoma with cornification Intrinsic cancer of the vocal cord Such tumors may be radiocurable but are usually not radiosensitive

Carcinoma of the anterior part of the tongue tends to be well differentiated but responds to radiation because of its accessibility

At the base of the tongue carcinomas are more undifferentiated and radiosensitive

TUMORS OF THE SALIVARY GLANDS

Mixed tumors of the salivary glands are radioresistant After incomplete removal the implantation of radium needles or radon seeds can effect a cure despite the radioresistant nature of the tumor Carcinomas of the salivary glands likewise respond unsatisfactorily to irradiation although occasional cures of epidermoid carcinomas of the salivary glands have been accomplished [3]

TUMORS OF THE THYMUS

The thymus shrinks rapidly when subjected to even small doses of radiation therapy owing

to the disappearance of its lymphoid elements The lymphoblastomas involving the thymus respond quickly and in the manner characterizing them throughout the body

In contrast the true thymoma is composed of cells derived from epithelium with thymocytes in variable numbers and has not been found to be radiosensitive or even to decrease significantly in size after the usual roentgen therapy This is due to the radioresistance of the epithelial part of the tumor

THYROID TUMORS

Although experimental data are not consistent the thyroid parenchyma like most secretory epithelium is radioresistant This inherent lack of response is evident in the various types of adenomas developing in the organ Destruction of the more radiosensitive cells with palliation and prolongation of life is more evident in the alveolar papillary and Hurthle cell types than in the giant and small cell varieties

Radioactive iodine is effective only in those tumors that are sufficiently differentiated to absorb and store the radioactive iodine injected

THE PARATHYROID GLANDS

The parathyroids withstand therapeutic exposures without clinical evidences of derangement The adenomas do not respond favorably and the incomplete data on such therapy for carcinomas do not indicate its use except for palliation

CARCINOMA OF THE BREAST

Most breast cancers are relatively radioresistant (see Vol IV)

CARCINOMAS OF THE ESOPHAGUS

Carcinomas of the esophagus are typically epidermoid rather malignant and radiosensitive Sterilization without mediastinitis or severe stenosis from breakdown of the esophageal wall is no longer a rarity Palliation is usually reasonably successful especially for the fungating and ulcerating tumors

BRONCHOGENIC CARCINOMA

From a theoretic consideration the undifferentiated types of bronchial carcinoma should be rather radiosensitive especially the epidermoid type Although such appears to be the case the poorly responsive tumor bed the proximity and early extension into cartilage and the limitation of exposure by the effects upon the pulmonary parenchyma all prevent the primary tumors of this region from being sterilized by radiation therapy If present bronchial obstruction and its complications may be reduced *Bronchial adenomas* are very radioresistant tumors

Metastatic Tumors of the Lung The sensitivity of the metastatic tumors to the lungs follows closely that of the primary tumors from which they are derived Because of the poor tumor bed and the limitation of exposure sterilization of even the most radiosensitive tumors is most difficult

THE GASTROINTESTINAL TRACT

Carcinomas are most radioresistant

The abdominal contents are well able to tolerate the exposures necessary to sterilize the great majority of lymphosarcomas with fields large enough to include the regional lymph nodes and apparent cures result

Leiomyosarcomas and comparable tumors are not more responsive to irradiation when situated in the gastrointestinal tract than they are in other locations

Carcinoids of the intestine are inherently radioresistant glandular tumors usually so well differentiated that they manifest slight tendencies of metastasis Adenocarcinomas conversely offer a poor prognosis since extensive metastases are usual—thus preventing complete removal of the tumor which is not only radioresistant but located where radiation therapy is limited by the sensitivity of the intestine

Polyps respond poorly or not at all as do leiomyomas lipomas and comparable tumors

The only tumor to give satisfactory results is the lymphosarcoma which responds in a manner similar to that noted in the stomach i e more favorably than in most other parts of the body

Corresponding to gastric carcinomas those arising in the colon are usually well differentiated Although some show evidence of being radiosensitive especially the polypoid forms radiocurability probably occurs only

uterus offers an unusually satisfactory bed for the radiation treatment of malignant neoplasms

Squamous cell carcinoma of the cervix is a radioresponsive tumor that yields gratifying results to radiation therapy

Carcinoma of the Endometrium

When the endometrial carcinoma is exposed to sterilizing intracavitary applications of radium there results a breaking up of the glandular structure swelling of the tumor cells pyknotic fragmentation of the nuclei necrosis leukocytic infiltration and slough' Sheehan *et al* [22] found that some months after the uterus was removed the tumor site was not evident However, the large exposures to the adjacent uterus caused a diffuse endometritis with necrosis of most of that layer The adjacent muscle fibers may become atrophied and a diffuse increase in collagen become evident but atrophy does not develop—the myometrium remaining normal in size or somewhat enlarged The radiation effects upon the vessels are evident especially near the source of irradiation The serosal surface is not altered At the internal os a necrotic plaque develops from the cauterizing effect of the irradiation

Tumors of the Vagina and Vulva

Carcinomas of the vagina tend to be poorly differentiated and should respond satisfactorily to irradiation but the thinness of the fibrous and muscular walls and the close proximity to the colon (most carcinomas arise on the posterior wall) limit the dose and make the treatment unsatisfactory Carcinomas of the vagina and cervix demonstrate the effect of the type of tumor bed upon the factors employed for irradiation and anticipated end results

The various sarcomas including the botryoid tumors of both children and adults exhibit a poor response to roentgen therapy

Carcinomas of the vulva manifest three important factors that limit the application of irradiation for their treatment (1) They are usually differentiated and hence radioresistant (2) the surrounding skin is moist and exposed to constant friction producing untoward sequelae from irradiation, (3) the large anatomic surface vitiates against administering an adequate dosage

TUMORS OF THE ADRENAL GLANDS

The adrenal glands appear to withstand even massive exposures without presenting significant necrosis Some loss of cholesterol content may be present but functional alterations are not detected after exposures within the therapeutic range

Adenomas of the adrenal cortex whether functional or not are surgical problems Carcinomas respond only moderately and do not appear to be curable except by complete extirpation Considerable palliation however may be expected temporarily from adequate exposures of deep roentgen therapy

One of the tumors that may be treated most successfully by irradiation is the more undifferentiated form of neuroblastoma—the sympathicogonioma Even multiple metastases in the liver may respond and fail to recur However when metastases occur in bone the tumors cannot usually be destroyed completely by irradiation The more differentiated tumors the sympathicoblastomas and ganglioneuromas do not respond to irradiation

The pheochromocytoma or chromaffin tumor requires surgical removal The malignant form of this tumor the pheochromoblastoma is rare and adequate data are not available but it does not appear to be radiocurable

CHAPTER 15

Biologic Effects of Ionizing Radiation

Charles L Dunham
and
L W Tuttle

With the development of atomic weapons and of the atomic energy industry during the 1940 s the radiation problem changed dramatically from one affecting at most a few thousand medical men patients and physical scientists to one that in its broader aspects could affect whole populations Consequently in the last few years much progress toward an understanding of the problem has been made While several theories concerning the interaction of ionizing radiation on biologic systems have evolved no single concept has been able to clarify adequately the entire sequence of events that follows exposure to radiation

Inasmuch as there is now available a series of excellent texts and reviews [2 3 5 6 8 9 10 11 13 14 15 17] dealing with the quantitative and theoretic aspects of radiation biology it is the hope of the authors that this chapter will serve a useful purpose if it is limited to a brief factual presentation of the interaction of radiation and matter and an attempt is made to develop the subject in such a way that the individual who is not trained extensively in the physical sciences may gain at least a qualitatively sound understanding of the field

THE NATURE OF IONIZING RADIATION

Ionizing radiation derives its name from its ability to produce a positively charged atom with a negative electron in its immediate vicinity by knocking an electron out of an atom This separation of electrical charges produces what is known as an ion pair The production of an ion pair requires the expenditure on an average of approximately 33 electron volts of energy Referring to Figure 15 1 it can be seen that the electromagnetic spectrum extends continuously from radio waves through the infrared the visible

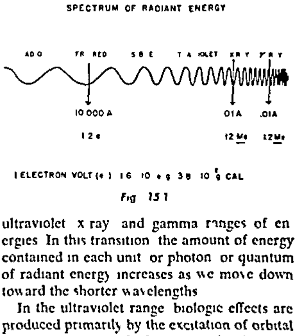


Fig 15 1

ultraviolet x ray and gamma ranges of energies In this transition the amount of energy contained in each unit or photon or quantum of radiant energy increases as we move down toward the shorter wavelengths

In the ultraviolet range biologic effects are produced primarily by the excitation of orbital atomic electrons to higher energy levels without a notable production of ion pairs However the existence of this metastable excited state is sufficient in many systems to produce chemical reorientations and subsequent biologic damage As we pass from the shorter ultraviolet energies into the soft x ray range the individual photon becomes increasingly energetic until finally it possesses more than the 33 electron volts of energy required for the production of ion pairs

Following the production of an ion pair the dislodged electron is rapidly absorbed by neighboring atoms and the positively charged atom and the molecule of which it is a part picks up a stray electron and once again becomes electrically neutral In this process electrical charges within the molecule are adjusted chemical bonds and even entire chemical groups may be altered

This description of the consequences of the formation of an ion pair by the dislodgment of an orbital electron and subsequent rearrangement and balancing of electrical forces is deceptively simple The biologic sequelae of such an event are out of all proportion to the energy supplied to the system

Before discussing in more specific terms the factors involved in the interaction of radiation and matter several broad generalizations shall be made concerning the effects of radiation on living systems

1 Radiation is nonspecific in its action Whereas many drugs and chemicals exert their influence upon specific and identifiable organs tissues or enzyme systems it has not been possible thus far in the case of radiation injury to pick out a particular weak link in protoplasmic organization that is specifically and exclusively sensitive to radiation There are of course variations in the relative sensitivity of specific organs to radiation and there is evidence that certain enzyme systems particularly those involving free sulfhydral groups are considerably more sensitive to the effects of ionizing radiation than others

2 All types of ionizing radiations exert *qualitatively* the same effect on living protoplasm Included in the term ionizing radiations are not only electromagnetic x rays and gamma rays but also the energetic positively charged alpha particles and protons negatively charged beta particles and uncharged neutrons The *quantitative* differences in the biologic effectiveness of these forms are due to the relative densities of the clusters of ion pairs that form along their paths as they are gradually slowed down with a transfer of their energy to the tissue

3 The effect of ionizing radiation on living cells is to damage them While there may be a lower dose limit below which no visible injury occurs and an intermediate dose range where apparent metabolic stimulation occurs there is no evidence that exposure to radiation however small, is anything but injurious

4 There is a *latent period* between the time of exposure to radiation and the appearance of signs of radiation injury This latent period in general varies inversely with the dose and the rate at which it is administered For exampl nausea may develop within a few minutes after exposure to a single large dose of radiation while many years may pass before cancerous changes or leukemia appear following a series of relatively small exposures

5 The *somatic* effects of radiation injury are reversible to a certain extent On the oth r hand *genetic* changes produced by radiation are irreversible and permanent

6 Most of the individual effects of ionizing radiation can be produced by one or another chemical or pharmacologic poison but no single substance can simulate all the effects of radiation Among the substances whose actions resemble in certain respects those of radiation are the nitrogen mustards carcinogenic sterols and hydrocarbons certain of the sex hormones hydrogen peroxide and others

THE INTERACTION OF IONIZING RADIATIONS WITH MATTER

Depending upon their energies x rays and gamma rays are absorbed by one or more of three mechanisms the *photoelectric effect*

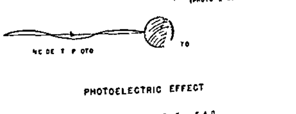
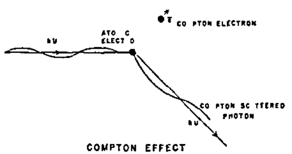


Fig 15 2

Compton effect and *pair production* Figure 15 2 illustrates the manner in which very soft x rays are absorbed by the photoelectric means with the production of an ion pair The photon transfers all its energy to the electron and disappears

In the Compton recoil absorption of rays

of higher energy as shown in Figure 15 3 the photon acts like a billiard ball and bounces off an atomic electron with which it shares its energy The deflected photon now containing less energy and having a longer wavelength

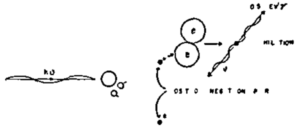


EL STIC COLL S ON OF A P OTO W T A SI GLE ATO C ELECTRON
E E GY S ED B ST UC ELECTRO A D DEGRADED P OTON

Fig 15-3

undergoes successive Compton recoil collisions until its energy becomes so reduced that finally it is absorbed in a photoelectric collision The dislodged electron may have received sufficient energy to act as an ionizing particle in its own right In Compton collisions the degraded photon may be deflected in any direction depending upon how it interacted with the electron This accounts for most of the scattering of x rays as they pass through matter

More highly penetrating rays such as gamma rays in the million-electron volt (mev) range are absorbed in part by what is known as pair production (The term pair production should not be confused with ion pair formation as previously discussed) In this type of absorption shown in Figure 15-4 the photon is completely absorbed in or near the nucleus of an atom As a result of this abrupt absorption of a high energy photon a positive and a negative electron pair are produced The positive electron or positron is extremely reactive in the sea of electrons that exists throughout matter and quickly reacts with a negative electron with the resultant annihila



PAIR PRODUCTION

HIGH ENERGY P OTON ABSORBED NEAR ATOMIC NUCLEUS PRODUC NG ONE POSITIVE AND ONE NEGATIVE ELECTRON POSITRON THEN REACTS W TH AN ELECTRON ANNIH LATION PRODUCES 2 QUANTA OF O 5 MEV γ RAYS

Fig 15-4

tion of the masses of both and the conversion of these masses into two half million volt gamma ray photons This reaction might be considered a miniature atomic explosion The two photons thus produced are then absorbed like any other gamma rays of the same energy

The relative importance of the three absorption mechanisms is shown in Table 15 1 from which it can be seen that the photoelectric mechanism predominates in the superficial therapy and the lower diagnostic x ray energy ranges while the Compton effect prevails in the 250 kv and higher therapy range of energies The pair production phenomenon is more of academic interest than of practical significance

TABLE 15 1 —Absorption of X and Gamma Rays

Radiation type	*Photoelectric absorption per cent*	*Compton absorption per cent*	*Pair production per cent*
Very soft	100		
Soft	75	25	
250 kv		99	1
Hard or gamma (above 1 mev)		98	2

ABSORPTION OF PARTICULATE IONIZING RADIATIONS

The particulate forms of ionizing radiation commonly studied and utilized in radiobiologic experimentation are alpha particles beta particles protons, and neutrons

Alpha particles are produced by the spontaneous transmutations of the atomic nuclei of the heaviest elements The particles are ejected at discrete velocities characteristic of the element involved They move at speeds up to one tenth that of light and have corresponding energies of up to 8 million electron volts An alpha particle is actually the naked nucleus of the helium atom stripped of its orbital electrons It has a mass of four and a positive charge of two Because of this characteristic of possessing a double charge heavy mass relatively large size and extremely high kinetic energy, alpha particles have a very short range in tissue and leave enormously dense ionization tracks which resemble solid cylinders of ion pairs Their maximum range in tissue is about 100 μ thus they are not able to penetrate the horny layer of the skin In air, alpha particles produce roughly 30 000 ion pairs per centimeter of path while in tissue the ionization density is equivalent to about 60 million ion pairs per centimeter of path

Beta particles are simply high speed electrons emitted by the nuclei of certain naturally occurring or artificially produced isotopes of the elements They have energies that may vary from almost zero to three or more million electron volts They behave just like the electrons produced by heated filaments cathode ray tubes or higher energy electron accelerators The beta particles emitted by the nucleus of a given element have a continuous spectrum of energies whereas alpha particles ordinarily are monoenergetic Thus the beta particles from radioactive phosphorus 32 have energies varying from almost zero to an upper limit of 1 7 mev with most of the particles having an energy of about 700 000 electron volts The velocity of a 1 mev beta particle is about nine tenths that of light Electrons and beta particles are absorbed by a combination of elastic and inelastic collisions with atomic electrons and nuclei Inelastic collisions account for the major portion of the energy lost by electrons of intermediate energy These collisions with atomic electrons produce ion pairs by removing the atomic electron from its orbit leaving a positively charged ion and a negative electron Of particular importance in the case of very high energy electrons inelastic collisions with atomic nuclei result in the production of a continuous spectrum of x rays

In air a 1 mev electron produces about 50 ion pairs per centimeter of track and has a range of several meters In tissue this particle will produce approximately 50 000 ion pairs per centimeter and have a range of several millimeters

Protons are hydrogen nuclei having a relative mass of 1 and a positive charge of one Ordinarily they are produced in cyclotrons and other particle accelerators but also occur as a result of the interaction of neutrons with tissue Because of their charge and their relatively great mass they produce very dense ionization in tissue somewhat comparable with that from alpha particles When accelerated to extremely high energies of over 100 mev protons have a range of approximately 10 cm in tissue During the last few millimeters of travel in tissue the density of ionization produced may be as much as 10 to 20 times that produced at the surface This characteristic suggests the possibility of using high energy protons in the treatment of deep seated cancer The use of high energy deuterons (heavy hydrogen nuclei) in therapy is currently being explored [16]

Neutrons are basic particles of matter having a relative mass of 1 and zero charge They may be produced by the interaction of alpha particles from the spontaneous disintegration of atomic nuclei of radium or polonium with the nuclei of beryllium or other light atoms Neutron sources may be prepared by mixing salts of the heavy radioactive elements with beryllium powder Neutrons are also released during atomic fission reactions and may be produced by the beams of cyclotrons and other high energy particle accelerators

At first glance one might expect the neutron because of its lack of electrical charge to be relatively harmless biologically However because its mass is great it may possess considerable kinetic energy Its lack of charge permits it to enter the nuclei of ordi

nary atoms and cause the ejection of energetic protons Fast neutrons that strike matter rich in hydrogen and living tissue is such a substance first are slowed down by a series of billiard ball collisions with the nuclei of the hydrogen atoms Each collision kicks out a recoil proton which in turn produces very dense ionization After the neutron has lost most of its kinetic energy in this manner and begins to wander about slowly as a so called *thermal* neutron it is *finally* captured by the nucleus of one of the ordinary atoms in the tissue Most frequently a nitrogen atom captures the slow neutron ejects an energetic proton and becomes radioactive carbon 14 Other possible neutron capture reactions result in the formation of radioactive isotopes of sodium phosphorus calcium sulfur etc

of x rays over a range of 12 to 850 kv produces energy absorption in soft tissue of from 40 to 100 ergs per Gm and up to 880 ergs per Gm in bone

The relative biologic effectiveness (RBE) of any given type of ionizing radiation is closely related to the density of the ionization produced in the biologic system The relative densities of ion pair tracks for some typical forms of ionizing radiation are shown in Figure 15 5 For a given form of ionizing radiation the mean ion density is inversely proportional to the energy of the radiation Thus for 30 to 180 kv x rays the mean ion density is 100 ion pairs per μ while for 1 000 kv x rays it is only 15 For gamma rays from radium it is 11 and for beta radiation from a 20 to 30 mev betatron only 8 The penetration in tissue however varies directly with the energy These two facts taken together account for the effectiveness of high energy radiation sources in the therapy of deep seated cancer The beta particle or the x ray with its initial high energy produces a relatively less dense ion track as it traverses the skin and other tissues overlying the tumor As it is slowed down by giving up energy to the tissue the ion track becomes more dense Ideally the radiation will produce its maximum ion density in the tumor

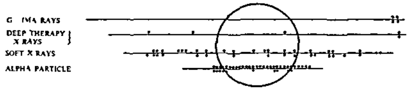


Fig 15 5 Separation of ion pair clusters in relation to size of a virus particle 27 mμ in diameter (*After L H Gray in N Howard Jones ed Applied Biophysics* New York Chemical Publishing Company Inc)

Because of this series of recoil interactions and capture the neutron is 10 to 40 times more effective depending upon the biologic system being studied than x or gamma rays giving comparable ionization figures as measured in instruments

RADIATION DOSAGE AND RELATIVE BIOLOGIC EFFECTIVENESS

The idea of using a radiation dose unit based on ionization produced in air was proposed as early as 1908 The definition suggested was that quantity of radiation which by ionization liberates one electrostatic unit of electricity per cubic centimeter of air under normal conditions of temperature and pressure Refinements of this definition of the unit called the roentgen were adopted at the International Congress of Radiology in 1928 and again in 1937 This established a precisely defined derived physical unit of dose In terms of biologic effect however this unit cannot be applied directly to ionization in tissues This results from the fact that one r

POSSIBLE MECHANISMS OF BIOLOGIC DAMAGE BY IONIZING RADIATION

Theories of the biologic action of ionizing radiation assume from the outset that only absorbed radiation is effective Thus a highly energetic photon or a charged particle may traverse substantial thicknesses of tissue without giving up energy and without producing injury

Of some historic interest is the *point heat* theory of Dessauer which postulated that the

energy of electrons produced during the ionization process was degraded by nonspecific collisions with protein molecules and that the energy was transformed into heat at isolated points The point heat theory fell short of accounting for so many of the sequelae of exposure to ionizing radiation that it failed to receive wide acceptance

During the 1920s the target or quantum hit theory was developed Within this theory it is postulated that there exists in the cell a specially sensitive volume or structure within which ionizations are biologically effective and outside of which ionization produces no effect The theory has proved valid in the study of gene mutation produced by the ionization of the gene molecule and the study of chromosome breakage following the passage of an ionizing particle through a chromosome It is probably valid when applied to a study of the inactivation of viruses and certain other macromolecules and the killing of bacteria by radiation Actually determinations of the sensitive volumes in the above systems by a study of inactivation or killing power in relation to radiation dose are in excellent agreement with molecular sizes as determined by other methods The target theory useful as it has proved in certain specific instances suffers from a number of general limitations First it is an oversimplification of the problem and does not take into account the fact that living cells can adapt to changes in environment even those produced by the radiation itself These adaptations may alter the susceptibility of the cell to injury in a manner that cannot be predicted In other words the theory is not applicable to types of injury from which recovery is possible Second the target theory makes no provisions for the biologic consequences of the action of ionization on water which makes up 80 per cent of the mass of protoplasm and which absorbs approximately 80 per cent of the energy from the radiation nor does it take into account biologic effects produced by radiation modified molecules of simpler organic metabolites

The failure of the target theory as originally conceived to account for many aspects of the radiobiology problem caused increasing attention to be directed toward studies of the radiochemical changes produced in water, and in aqueous solutions of metabolically important organic substances Progress in this field came in the late 1930s and early 1940s largely as a result of fundamental studies of British investigators [10, 14] The theoretic concepts relating radiochemical changes in nonliving systems to the biologic effects of radiation are still evolving While an impressive amount of information has been accumulated in recent years on the chemical effects of ionization it would be premature at this time to make any broad generalizations purporting to tie the complex series of biologic changes produced by ionization to the influence of any specific radiochemically altered metabolites It is increasingly apparent however, that the radiochemical approach is the one most likely to provide a satisfactory explanation for the tremendously complex biologic changes that follow the exposure of living matter to ionizing radiation The term 'chemical effects of radiation includes the effects that might be expected as a result of the formation of such things as peroxide, activated molecules and free radicals

Since water is the principal component of protoplasm in terms of number of molecules the study of radiochemistry logically should begin with an investigation of the effects of radiation on water The following discussion is based largely upon the concepts of Weiss [14] The action of ionizing radiations on water results ultimately in the production of hydroxyl (OH) free radicals and hydrogen atoms (H)

In the ordinary water molecule the six orbital electrons of the oxygen atom are shared with the single orbital electrons of two *hydrogen* atoms to form the chemically stable octet arrangement H O H In the ordinary chemical ionization or dissociation of water one hydrogen atom can break away from the remainder of the molecule leaving its electron behind and thus forming a hydrogen ion *(H)* and leaving a hydroxyl ion ($\bar{O}H$) The stable octet arrangement of electrons about the oxygen atom is intact and the two ions thus formed are relatively inert and exchange readily with other water molecules Under the influence of ionizing radiation however the

energy supplied is sufficient to cause a hydrogen atom to break away from a water molecule to form a neutral hydrogen atom with a single orbital electron and leave behind a neutral hydroxyl group with only seven orbital electrons around the oxygen atom Since the laws governing chemical stability require that the hydrogen atom have two orbital electrons and the oxygen atom eight both groups become enormously reactive chemically A series of electron transfer processes may be summarized as

$$HOH + \text{radiation} \rightarrow H + OH$$

Free radicals and atoms owe their chemical reactivity to the fact that they can lower the energy barrier or peak that must be crossed in order for a chemical reaction to take place The existence of free radicals in the presence of complex normal molecules facilitates the exchange of atoms and chemical groups with the formation of new free radicals and makes possible a chain reaction conceivably affecting hundreds of molecules The probable extension in space of such reaction chains may assume proportions on the order of one ten thousandth to one thousandth of a centimeter Chemical exchanges and rearrangements of this magnitude could be extremely important to the functions of organized biologic systems It is believed that the hydroxyl free radical is of the greater importance in the propagation of chain reactions

In the presence of dissolved oxygen free radicals in an aqueous system promote the formation of hydrogen peroxide (H_2O_2) which in itself is a cellular poison but which also can decompose to form hydroperoxyl free radicals The production of hydrogen peroxide when water is irradiated in the presence of oxygen has been demonstrated chemically

In living systems ranging from microorganisms to mammals [4] it has been shown that the oxygen tension prevailing at the time of the irradiation markedly influences its biologic effects In the absence of oxygen or under reduced oxygen tension biologic injury is significantly decreased

In view of our knowledge of the changes in chemical structure that can be brought about by the presence of free radicals and knowing the profound differences in pharmacologic action that may result from slight alterations in a drug molecule it is not at all fantastic to speculate that radiation induced changes in the molecules of normal metabolites may produce antimetabolites and thus account for much of the biologic effect of ionizing radiations

FACTORS AFFECTING RADIATION INJURY

It would be inappropriate in this chapter to dwell at length on the ultimate effects of ionizing radiation on tissue The interest of the cancer therapist is principally in the death of cancer cells and how to accomplish this with a minimum of damage both early and late to adjacent and overlying normal tissues Newer technics with the high energy sources rotational therapy and the like now permit concentration of the dose in depth so the problem of damage to skin and other tissues overlying tumors is largely overcome There still remains the fact that there is only a small margin of safety in the dose of radiation needed to kill cancer cells and that which will kill normal cells or of perhaps even more importance produce ultimately harmful late effects such as constricting cicatrization telangiectasia with its tendency to bleeding and malignant degeneration

Although the ionizing event is practically instantaneous the effects in biologic systems are not immediately apparent This is strikingly illustrated by the fact that members of the staff of the Nagasaki Medical School who survived the first few minutes after the atomic bomb exploded took refuge on a hill several hundred yards farther away with no particular difficulty A few hours later several sickened and in a few days were dead Others did not have important symptoms for a matter of two to three weeks

The same is true with radiation applied locally Depending on the dose administered and the type of tissue or tumor irradiated hours days and even weeks may elapse before the effect is apparent

For example let us take such an obvious effect as cell death With extremely high doses of radiation cells may be killed immediately On the other hand with more moderate doses the cell may die during its next attempt at

mitotic division When this occurs chromosomal abnormalities are readily demonstrable as a rule Some irradiated cells undergo a few apparently normal divisions and then die A possible explanation of this phenomenon might be as shown in Figure 15 6 Let us assume that a single gene controls the production of a single characteristic or biochemical

DELAYED CELL DEATH

FOLLOWING RADIATION

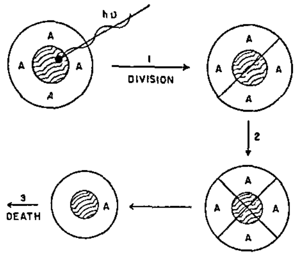


Fig 15 6

function or enyme system within the cell and an ionizing event knocks out a gene controlling the production of a hypothetical substance *A* that is essential for the normal functioning of the cell and is free in the amount of four basic units The cell may then undergo two normal divisions by sharing the substance *A* among the four daughter cells thus produced Each daughter cell then possesses only the minimal amount of *A* that permits normal function Upon attempting to complete a third cellular division the cell dies

Among the most striking things about radiation injury whether incurred locally or sustained by the whole body are the marked individual differences in susceptibility of the irradiated systems With whole body irradiation in mammals a factor of two is not uncommon in comparable animals of the same species The same is true in general for apparently similar normal cells or tumor cells while among different cell types a factor of 10 000 may pertain between the minimum lethal dose and that which will kill all the cells In radiation therapy it is the few remaining extremely resistant malignant cells that baffle the radiotherapist Some of the apparently most radiosensitive tumors are distressing examples of this It is relatively easy to cause the tumor to melt away because of the extreme sensitivity of the great majority of the cells Nevertheless a few weeks or months later the neoplasm is again flourishing

Perhaps the greatest hope for a substantial improvement in the treatment of tumors by radiations evolves from the fundamental observation that the radiosensitivity of those tissues that normally exist in a condition of hypoxia or low oxygen tension is increased by factors of from one and one half to three when the tissues are irradiated while in an atmosphere of pure oxygen at increased pressures Experiments by British investigators [7] have shown that the destruction of transplantable animal tumors by radiation is markedly increased when the animals are placed in a pressure chamber at three atmospheres oxygen pressure during irradiation Subsequent clinical trials in which cancer patients were given radiation therapy while maintained in a pressure chamber at three atmospheres oxygen pressure have been encouraging

The reversibility of the biologic effects of ionizing radiation is more apparent than real Following radiation injury a tissue may soon be functioning normally and present a normal histologic appearance This has been accomplished however not by actual recovery of the injured cells but by replacement by regeneration from surviving normal cells

It is true that there are degrees of radiation injury for which the individual cell can compensate or correct, apparently living out a normal life span Furthermore there is good experimental evidence that repeated small doses of radiation although very definitely cumulative in effect do permit of some recovery after each dose In this way it may be possible for an animal or tissue to survive a total dose several times that which if it had been given all at one time would have proved lethal or extremely damaging On the other hand every exposure of normal tissue to ionizing radiation leaves that tissue more sus

ceptible to radiation injury than it was before while from the genetic standpoint once a gene has been altered by radiation the altera tion is to all intents and purposes permanent

THE NATURE OF RADIATION INJURY

The characteristic effects of radiation in jury in mammalian systems can be sum marized as follows

1 *The cell* Depending on the severity of the injury the cell will demonstrate in vary ing degree a number of the usual nonspecific signs that accompany injury from a variety of causes These include such things as altera tions in permeability of the cell membrane vacuolization and liquefaction of the cyto plasm fragmentation of the nuclear substance and coagulation of chromatin (More subtle changes have been shown by means of tissue enzyme studies to occur following doses of radiation as low as a few r [1])

A great deal of attention has been given to the changes that occur in the cell nucleus because they are most likely to give a key to the late effects of radiation It has been amply demonstrated that damage to genes is irreversible once it has occurred With regard to chromosome damage it appears that detect able effects on chromosomes are likewise irreversible and as far as germ cells are con cerned the results are lethal or are manifested as semisterility

Nucleoproteins as such especially as they occur in viruses and bacteria are relatively resistant to ionizing radiation It takes many thousands of r to destroy microorganisms Nevertheless nucleoprotein metabolism is seri ously interfered with by relatively moderate dosages of radiation

2 *Tissues and organs* The effects of ioniz ing radiation on tissue masses and organs is essentially a summation of the alterations described above The severity of the injury will depend on the radiosensitivity of the tissue the magnitude of the dose the length of time elapsed during administration of the total dose and the reparative powers inherent in the particular tissue in question The radio sensitivity of any given tissue or mass of cells is not a constant but will vary with its meta bolic activity the stage of growth and the age of the cells concerned There will be more or less repopulation by normal cells depending on the regenerative powers of the surviving cells For example it can be calculated that a single dose in the neighborhood of 30 r to mice would result in the appearance of twice as many mutations as would be expected to occur spontaneously [12] Several hundred r of radiation to the gonads will cause per manent sterility A similar dose to lymphoid tissue will wipe out all but the stem cells which promptly repopulate the node while a like dose to the normal skin will not even produce an erythema or have any permanent effect other than a lowered resistance to further irradiation

An important and unique characteristic of the repair processes that follow radiation necrosis is that cell death is occurring simul taneously with efforts at repair This may go on for weeks months and even years The inability of the tissue to provide itself with an adequate and stable blood supply is of great significance and contributes to the picture of repeated healing followed by breakdown so characteristic of severe local radiation injury The end result as is well known may be neoplasia

There are several mechanisms that con tribute to favorable results in treating cancer with ionizing radiation Probably the least important one is immediate cell death unless literally cauterizing doses are to be used Delayed cell death at the time of the first few mitoses following treatment plays a very important role This effect to all intents and purposes sterilizes the cancer cells most sus ceptible to chromosome damage resulting in their ultimate disappearance Other factors that contribute to the destruction of the tumor include damage to the blood supply especi ally where large doses are used and the less well understood biochemical changes that alter the cell metabolism

WHOLE BODY IRRADIATION

Brief mention should be made of the effects of ionizing radiation when administered to the whole body It appears that doses of a few hundred r or greater whether received as at Hiroshima and Nagasaki all at once or over a period of years favor the development of leukemia For man the median lethal dose

of gamma rays is in the neighborhood of 400 r This dose is not known to produce regularly serious permanent radiation injury to any organ of the body, excepting of course the germ cells Yet 50 per cent of persons receiving such radiation will die On the other hand this dose will temporarily wipe out lymphoid and hemopoietic tissue and destroy some of the intestinal epithelium Recovery of the latter takes place in a few days, while it may be several weeks before the former tissues are fully restored If a person survives the acute illness with its pancytopenia its hemorrhagic state and its absence of the normal mechanisms for combating bacterial invasion he is once again an apparently normal individual Nevertheless an increased incidence of leukemia has occurred among these survivors Whether there will with the passage of time be a significant increase in other forms of malignancy is not known The radiation cataracts that have appeared among certain individuals all of whom were within 1 100 meters of ground zero at the time of exposure and consequently subjected to neutron exposure in addition to gamma rays are incidental to the whole body exposure and not peculiar to it In other words the same amount of neutron and gamma radiation to the eyes only would have produced the same effects Similarly genetic effects would be expected to reflect directly the dose of radiation received by the germ cells

It is only recently that sufficient data have been accumulated to show that shortening of life span and accelerated aging result from exposure to ionizing radiation [18] The following tabulation shows the life shortening in radiologists who have received cumulative doses in connection with their occupation of approximately 1000 r

	Average Age at Death
Physicians having no known contact with radiation	65 7 years
Specialists having some exposure to radiation (dermatologists urologists etc)	63 3 years
Radiologists	60 5 years
U S population over 25 years of age	65 6 years

It is apparent that partial body exposures of human beings to approximately 1 000 r even when administered very slowly over a period of many years shortens life expectancy by about 8 per cent

THE NEED FOR MORE INFORMATION

In the past decade we have come a long way toward beginning to understand the action of ionizing radiations on biologic systems The increasing attention given to the effects on the intra and extra cellular fluid environment of cells and the better understood metabolic processes has given a number of helpful clues as to the mechanisms involved We know that radiation is much more lethal to virus particles when in dilute solution than when the virus is irradiated in the dry state The studies of the effects of radiation on water and sulfhydryl enzyme systems have been particularly noteworthy Meanwhile a great deal has been learned about the end results of exposure of biologic systems to various amounts of ionizing radiation We have learned how many r of one or another form of radiation are needed to produce genetic change cause cell death neoplasia and the like in a variety of organisms Between these two realms of knowledge however there remain large gaps to be filled in

With the tremendous impetus of the atomic energy programs both here and abroad the development of our knowledge of the biologic effects of ionizing radiation has become of more than mere academic interest The implications of atomic warfare plus the ever increasing use of ionizing radiations in the laboratory in the clinic and in industry demand that we understand the actions of ionizing radiation in all its forms on living matter Only with this knowledge can we intelligently protect those who work with radiation treat radiation injury and exploit radiation in the diagnosis and treatment of cancer

Clinical Application of Roentgen Rays

CHAPTER 16

The Clinical Application of Low-Voltage, Short-Distance X-Ray Therapy*

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and
Richard H Chamberlain

The uses of low voltage short distance x ray therapy are limited to the treatment of those accessible tumors in which it is desirable to limit the depth penetration of the x ray beam Arrangements to maintain a short distance between the x ray tube target and the tissue surface limit the penetration by inverse square law relationships The use of low voltage potentials accomplishes a similar objective by producing x ray beams of longer average wavelength that have increased absorption in the superficial layers of tissue The wavelength principle can be extended by altering the inherent and added filtration as developed in recent x ray tube designs employing thin beryllium windows for transmission of the useful beam It is perhaps somewhat more accurate to refer to this field of therapy as long wavelength short distance x ray therapy but various forms are known as contact therapy and by the name of the equipment used

A tumor that is superficial or accessible through a natural body orifice may be considered for this form of treatment if it is possible to cover the area of the tumor and if its peripheral permeation falls within the range of penetration available with the x ray apparatus The usual limitation of x ray therapy to tumors suitable for radiation therapy must still prevail as the concept of low voltage short distance therapy is a quantitative one in respect to the radiation delivered to tissue Some extension of usefulness is possible by making deeper tumors accessible through surgical incisions

From the physical aspect an ideal pattern of tissue irradiation would be achieved if a uniform and homogeneous dosage of radiation could be delivered to the chosen area without appreciable radiation to surrounding or deeper tissues Such control is not possible but in many ways low voltage short distance x ray therapy most closely approaches this objective and has other advantages over surface radium technics and other radiation methods in respect to ease and quickness of treatment radiation safety precision in application versatility and reproducibility

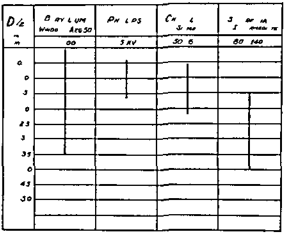


Fig 16-1 Ranges of D ½ values for low voltage short distance equipment (After Smithers)

* Editorial Note Since the preparation of this chapter several minor changes have been made in the technics and indication for the use of low voltage short distance x ray therapy

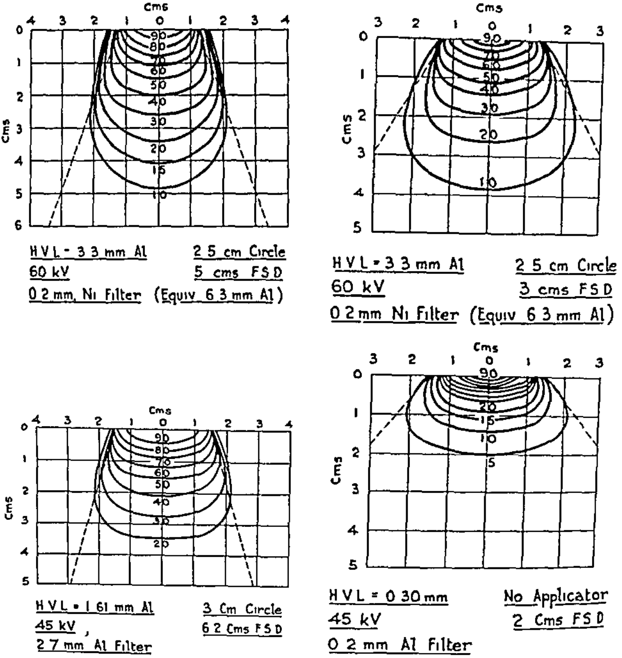


Fig 16-2 Isodose curves for low voltage short-distance therapy (*upper left and right*) Chaoul tube (*lower left and right*) Philips tube (courtesy W V Mayneord)

PHYSICAL CONSIDERATIONS

In describing the physical distribution of radiation delivered the usual expressions of kilovoltage and half value layer are inadequate because of the marked alterations introduced by small changes in distance filter and field size or shape as well as by voltage A more suitable description proposed by Mayneord and Smithers expresses the effective penetration of the radiation in terms of the depth of tissue at which the dose is reduced to one half of its surface value This is known as D½ in centimeters and for specific equipment may be varied over a fairly wide range (Figure 16 1) More complete and satisfactory description of dosage distribution is afforded by isodose contours which are the only means by which all the variables are adequately included A group of representative isodose curves is shown in Figure 16 2

The rapidity with which the dosage falls off after reaching the D½ point is of importance in limiting the radiation to the desired area This may be expressed as the ratio be

tween the 90 per cent absorption depth and the 50 per cent absorption depth as proposed by Jennings [11] in his fall off ratio This is illustrated for a variety of voltage and filter conditions with a beryllium window tube in Figure 16 3 It is also shown in the isodose contours

EQUIPMENT

The clinical use of the short range principle was described by Schaeffer and Witte in 1929 and Zimmer described an intracavitary tube as early as 1932 In present usage the Siemens Monopan the Philips contact and cavity apparatus and beryllium window tubes of Machlett Laboratories and the General Electric X Ray Corporation are most widely known

The tube illustrated in Figure 16 4 from the designs of Chaoul and Adam is used in the Siemens Monopan apparatus and clinical treatment with it is sometimes known as Chaoul therapy Energized by a 60 kv generator the cathode emission strikes the inner surface of a nickel foil target 0 15 mm thick and the x ray beam used for treatment is transmitted through the target a layer of water used for cooling and then through another metal foil that encloses the water jacket This arrangement also grounds the target and permits application at very short target skin distances but is achieved at the expense of high inherent filtration It is not possible to lower the voltage much below 60 kv without too much reduction in the intensity of the beam and most of the longer wave lengths are absorbed by the inherent filter (H V L 3 3 mm Al) In clinical use there fore the limitation of depth penetration is ob tained largely through the short distances used and their inverse square law advantage Applicators for 1 5 3 0 and 5 0 cm target skin distance are most useful and are available in numerous sizes and shapes An output of

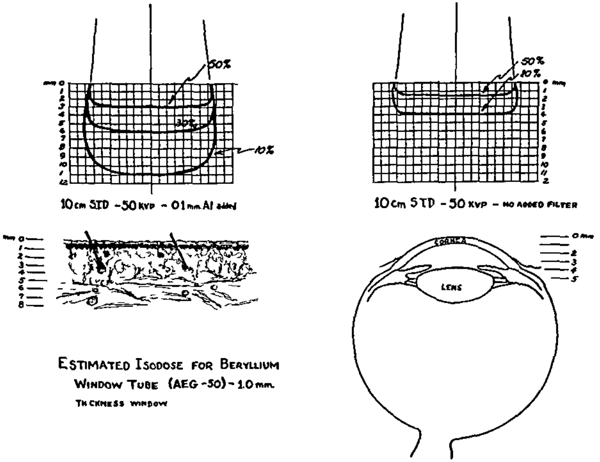


Fig 16 2 (Contd) Beryllium window tube

HVL IN MM. OF AL	10CM STD 3.0CM DIAMETER PORTAL AEG 50 TUBE							
	90% ABSORPTION mm. w	50% ABSORPTION mm. w	FALL OFF RATIO 90%/50%	KVP 50	30	20	10—2	ADDED FILTER mm AL.
1 03	58 5	15 8	3 7	50				3 22
1 30	42.5	12 0	3 55		30			3 22
0 94	43 2	10 8	4 0	50				1 06
0.66	31 2	8 2	3 80		30			1 06
0 505	34 1	7 1	4 80	50				0 56
0 44	21 0	6 0	3 50			20		1 06
0 305	24 7	5 5	4 50		30			0 56
0 28	16 0	3 85	4 15			20		0 56
0 165	21 0	3 5	6 0	50				0 25
0 155	15 9	3 0	5.3		30			0 25
0 145	10 7	2 15	5 0			20		0 25
0 105	11 7	2 10	3 6	50				0 10
0 10	9 6	1 90	5 05		30			0 10
0 09	7 4	1 55	4 8			20		0 10
0 08	8 6	1 55	5 55	50				0 05
0 075	7 2	1 40	5 15		30			0 05
0 07	5.1	1 10	4 90			20		0 05
0 07		1 05		50				0
0 06		0 90			30			0
0 057	3 68	0 70	5 25			20		0
0 042	2.14	0 63	3.4				10	0 10
0 035	1 89	0 52	3 65				10	0 05
0 026	1 50	0 36	4 15				10	0
	1 15	0 29	3 95				8	0
	0 81	0 22	3 65				6	0
	0 60	0 18	3.35				5	0
	0 40	0 14	2 85				4	0
							3	0

Fig 16 3 Beryllium window tube factors (Courtesy R A Jennings Royal Northern Hospital London)

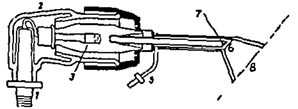


Fig 16-4 Diagram of Chaoul tube (1) connection to transformer (2) water jacket (3) cathode (5) water supply (6) window (7) anode (8) surface of area treated

approximately 1 000 r min can be expected at 1 5 cm target skin distance with 60 kv and 4 0 ma Other tubes for intracavitary use can be obtained with the Siemens apparatus using a conical target that produces a radial distribution of radiation similar to the isodose pattern of a radium cell

Another type of design is shown in the Philips tube illustrated in Figure 16 5 In this tube a ring filament emits the cathode stream

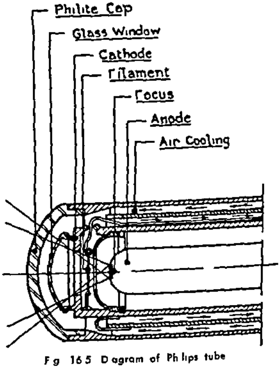


Fig 16 5 Diagram of Philips tube

that impinges on the front surface of a central target The useful beam is transmitted only through a thin glass front window and a plastic cap which contains the cooling flow of air that is passed across the front of the tube A lower voltage 45 kv is employed and the inherent filter is considerably reduced so that half value layers as low as 0 2 mm Al are made it possible to use beryllium in windows as thin as 1 0 mm inserted in the x ray tube for transmission of the useful beam Practical designs of such tubes manufactured by the General Electric X Ray Corporation and Machlett Laboratories are now in use and a diagram of a Machlett OEG 60 tube is shown in Figure 16 6 In this tube the cathode

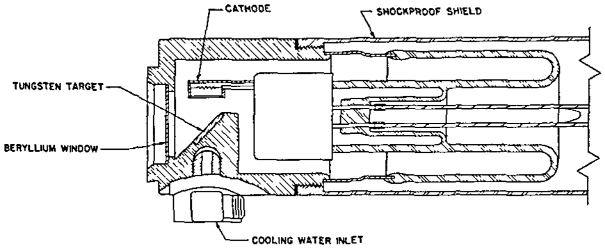


Fig 16-6 Diagram of beryllium window tube—Machlett OEG 60

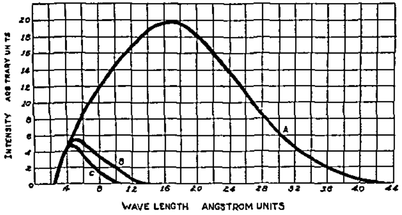


Fig 16 7 Transmission of radiation by beryllium window tubes

obtained Outputs of approximately 8 000 r min may be expected with 45 kv at 1 8 cm T S D and 2 0 ma The minimum target skin distance is 1 8 cm and the usual assortment of cones is for 2 0 cm 4 0 cm and greater distances Added filters of 1 0 and 2 5 mm of aluminum are supplied Within the ranges so provided the depth penetration of the radia tion can be adjusted to the tumor by either inverse square law effect alteration in effec tive wavelength or both

Technical advances in recent years have

stream is emitted by a laterally placed cathode and impinges on a target set at 45 from the end face through which the useful beam emerges after having traversed only the beryl lium window Cooling is effected by water that is pumped through the back of the target The output of tubes of this type is astonish ingly high because of the large proportion of long wavelength radiation transmitted (Figure 16 7) and because tube currents as high as 50 ma may be employed with voltages of 10 to 100 kv for different tubes As much as 2

change in cellular maturation [21] Unfortunately, this approach does not seem to be practical on present evidence for routine use It is highly desirable to give adequate radiation treatment in the first course, for the treatment of recurrences is never as satisfactory as the primary result In the limited volumes of tissue irradiated with the low voltage short distance method tissue recovery is good even with rather high dosages and one can carry the treatment to levels of 10 000 maximum and 8 000 minimum r tissue in small fields if the physical calibration is reliable Tumors of unusual resistance may be encountered but most failures are attributable to errors in technic or judgment With proper attention to details the long term results are comparable or superior to alternative surgical or radium methods and usually considerably better from the cosmetic standpoint

CANCER OF THE SKIN

Any form of low voltage short distance apparatus may be chosen for treatment of basal cell or squamous cell epitheliomas of the skin if it will furnish suitable D½ or isodose contours to the planned zone of treatment If the tumor projects above the surface of the skin initially and regresses during treatment, it may be advantageous to alter the isodose plan in the latter part of the treatment course Presuming that the area is not too large and that daily increments of about 500 r (in air) are given a small tumor may require 6 000 tissue r maximum and 4 500 tissue r minimum in the tumor itself The upper limit of treatment may be 10 000 tissue r maximum and 8 000 tissue r minimum In each of these instances the D½ 3 000 r in the first instance and 5 000 r in the second will be adjusted to the limits of the reasonable margin beyond the tumor The first dosage scheme may be chosen for a basal cell epithelioma or used for a patient who shows a quick rise of severe skin reaction and early reduction in induration of the tumor (Figure 16 9) The higher dosage level may be used for a rather resistant squamous cell carcinoma When multiple portals are required or unusually large single portals are chosen the total dosage may be reduced

Fig 16 9 Basal-cell carcinoma of skin (*left*) before treatment (*right*) after treatment (Chaoul tube)

TABLE 16 1—COMPARATIVE EFFECTIVENESS OF X RAY AND RADIUM THERAPY FOR BASAL CELL AND SQUAMOUS CELL CARCINOMAS OF SKIN

		Number of cases	*Net number of cases*	*Number symptom free*	*Number recurrent*	*3 year symptom free rate per cent*
Basal cell carcinoma of skin	Radium	2 534	2 151	1 575	576	63
	X ray	316	217	200	17	92
Squamous cell carcinoma of skin	Radium	952	801	545	256	56
	X ray	138	108	74	34	69

20 to 30 per cent The results of treatment of a group of cases reported by Smithers are shown in Table 16 1 and are compared with results in a series of cases treated with surface radium A more favorable group of squamous cell carcinomas considered to be Stage I showed better results with low voltage short distance therapy 80 per cent being symptom free at the end of five years

Epitheliomas that appear to rise from sweat gland or skin adnexal origin sometimes show unusual resistance to irradiation and if their histologic nature is identified surgical removal may be considered for primary management unless the location or other features outweigh this consideration In the definitive management of malignant melanomas surgery is by far the treatment of choice and radiation therapy should be used only if the object is palliative regression of tumor mass and not cure

CANCER OF THE NOSE AND EAR

The underlying cartilage and bone in these sites modify the spread of superficial tumors and introduce new problems of radiation reaction in these special tissues When the tumor has not invaded cartilage or bone, the method of treatment can be planned as for the skin in general When the tumor has invaded cartilage it is still possible to achieve good results but extensive tumor destruction of cartilage may result in defects that heal poorly if this can be anticipated it is often preferable to employ surgery as the primary treatment It is in extensive superficial spread of tumors that the particular advantages of low voltage short distance therapy are manifest The nose is a frequent site of epitheliomas arising from sweat gland or skin adnexal origin

CANCER OF THE EYE

The precision of low voltage short distance therapy is unusually valuable about the eye where treatment of the lid sclera or surrounding skin may be needed while destroying as little normal tissue as possible both for function and for appearance The lens must be protected as much as possible and similar consideration given to the naso-lacrimal apparatus For tumors of the lid the globe of

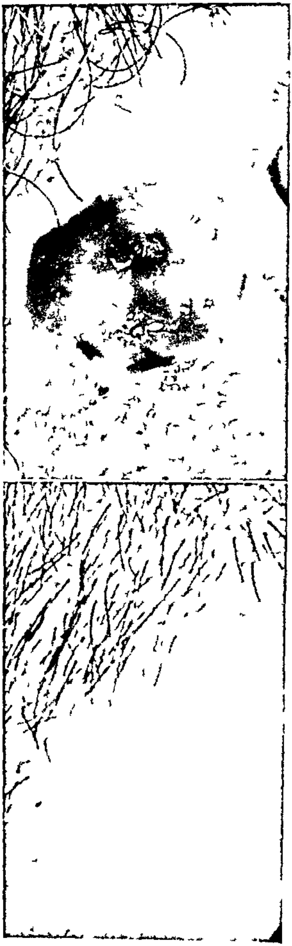


Fig 16-10 Prickle-cell carcinoma of the skin (upper) before treatment (lower) after treatment (Chaoul t be)

the eye should be shielded with lead or heavy metal cups inserted beneath the lid The direction of the beam and the choice of radiation factors can also be used to reduce the radiation to the deeper structures Some postradiation atrophy of the skin, loss of eye lashes and similar changes are to be expected, but ectropion, interference with lid closure tearing and similar complications are reduced to a minimum and their occurrence is related to the extent of the original tumor destruction rather than to the postradiation effects In treating tumors of the inner canthus some radiation to the naso lacrimal apparatus will be unavoidable but complications are not to be expected unless the tumor has invaded the duct or sac Malignant tumors of the sclera can be treated more safely and effec tively by low voltage short distance technics than by any other method The beryllium window tubes are most versatile in this in stance in offering a range of D½ values that gives the least irradiation to the lens

CANCER OF THE LIP

Malignant neoplasms of the lip are un usually accessible and if the lip can be pulled out almost any form of x ray therapy can be applied The low penetration concept can be used to advantage however in planning cross firing portals through two or three axes and the ease with which the multiple fields may be applied is helpful Furthermore, the time required for each treatment is short and this helps in avoiding motion of the patient during therapy With multiple portals a range of tissue dose values within the tumor, of 6 000 r minimum to 8 000 r maximum is usually adequate, given within 2 to 3 weeks Five year symptom free results have been reported by Smithers for 74 per cent of Stage I squamous cell carcinomas of the lip

CANCER OF THE VULVA

It has been our experience that the skin of the vulva is a poor site for radiation therapy of any type and that excessive radiation re action and intolerance can be expected This has been true for low voltage short distance methods as well as for conventional irradia tion and surgical excision is to be preferred

Fig 16 11 Squamous-cell carcinoma of tragus of ear (*left*) before treatment (*right*) after treatment (Chaoul tube)

CANCER OF THE RECTUM AND BLADDER

In some European clinics and at a few centers in the United States low voltage short distance therapy has been used for cancer of the bladder and rectum by applying it through surgical incisions and some rectal carcinomas may be accessible to direct treatment without surgery [7 8 14] In the latter case there are difficulties in accurate placement and in esti mation of the extent of the area that needs to be covered both of which have been suf

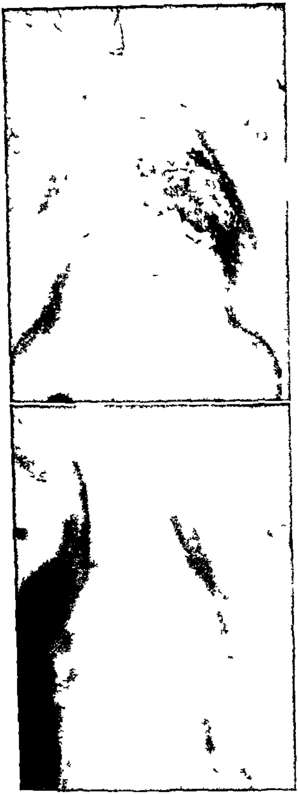


Fig 16-12 Basal-cell epithelioma of nose (upper) before treatment (lower) after treatment (Chaoul tube)

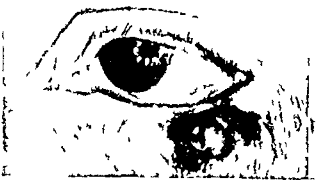
ficient drawbacks to dampen enthusiasm for more widespread use When surgical incisions are used the tube may be encased in sterile sheaths but all the treatment must be given in a few applications and the preparations for therapy are rather cumbersome We have had little experience in this field

CANCER OF THE CERVIX

The direct application of radiation to the cervix [13] is feasible with any one of the forms of apparatus described and the conical tip Siemens tube was designed for such use Nevertheless the treatment of carcinoma of the cervix is seldom a local problem within the scope of the effective radiation from these tubes and more adequate coverage is offered by radium and more penetrating x ray methods In deciding on a plan of treatment adapted to the anatomic relationships in the pelvis we have thought that greater flexibility was afforded by other means

HEMANGIOMAS OF THE SKIN

Cavernous hemangiomas and strawberry types of these benign growths respond very well to moderate doses of radiation therapy and low voltage short distance therapy has been of particular usefulness in these cases because of its safety and precision There is little danger of delivering harmful radiation to underlying growing parts when the penetration is properly adjusted to the dimensions of the hemangioma and the total amount of treatment is kept to moderate levels Usually increments of 200 to 300 r repeated at intervals of 6 to 10 weeks will produce satisfactory regression at total dosages not in excess of 1 500 r The best results are obtained if treatment can be started in the first few weeks of life Sufficient time must be given for response to each treatment to be evaluated and the end result may not be manifest for 8 to 12 months or longer The high dose rate of most of the equipment is helpful in treating infants in a short period of time and with immobilization by wrapping and sandbags as well as holding the applications can be given exactly to the desired area The protection of personnel must be observed but is relatively easy In our experience with over one thousand infants over a period of twenty years the end results have been most satisfactory Only one case of radiation injury to an underlying epiphysis has been seen



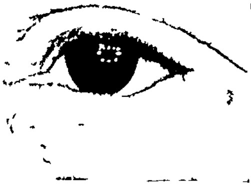
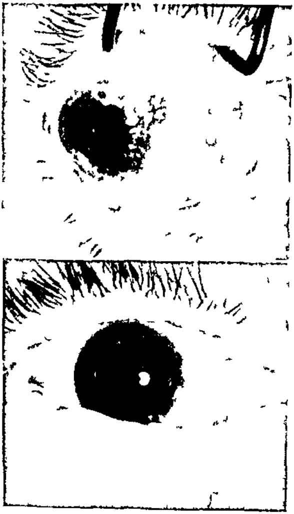


Fig 16 13 Basal-cell epithelioma of lower lid (*left*) before treatment (*right*) after treatment (Chaoul tube)



OTHER NONCANCEROUS CONDITIONS

The principles of low voltage short distance x ray therapy have applications to radiation therapy of other nonmalignant conditions such as vascularization of the cornea interstitial keratitis vernal conjunctivitis and other benign lesions of the eye They have also been used for some benign skin diseases In the treatment of all benign conditions it is necessary to be satisfied that the indications are adequate for radiation therapy and then to use the method that will furnish the best distribution of radiation possible It is in this respect that the flexibility and easy adaptability of the low voltage short distance apparatus is most desirable In the treatment of the cornea the favorable superficial radiation of beta sources such as radon or strontium 90 may be duplicated by beryllium window x ray with the added features of being able to define the field more precisely giving the treatment in a shorter time without motion of the eye and having better calibration of the amount of radiation given with the latter source

Fig 16-14 Basal-cell epithelioma of sclera (*upper*) before treatment (*lower*) after treatment (beryllium window tube—Machlett AEG 50)

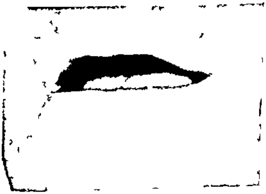


Fig 16-15 Squamous-cell epithelioma of lip (*left*) before treatment (*right*) after treatment (Chaoul tube)

CHAPTER 17

The Clinical Application of Medium-Voltage X-Ray Therapy (140 to 400 Kv) in Cancer Treatment

Frank J Borrelli
and
R Vincent Grieco

INTRODUCTION

Medium voltage x ray therapy is the form of roentgen irradiation most frequently used in the treatment of cancer and is the type of irradiation that has been most extensively studied

The terms low medium and high voltage therapy are arbitrary designations that indicate either the clinical type of treatment administered or the physical nature of the equipment employed

Clinical designations	*Physical or equivalent designations*
1 Contact therapy	45 to 60 kv
2 Superficial therapy	Low voltage 80 to 140 kv
3 Deep therapy	Medium or high voltage 140 to 400 kv
4 Deep therapy	Supervoltage 700 to 2 000 kv or higher

Medium voltage x ray has a wide spectrum of application because the nature of its beam permits the deliverance of ionizing radiations to most locations that are the sites of malignant neoplasms In fact it would seem that a renewed appreciation of medium voltage x radiation therapy has evolved as a result of shortcomings of certain newer technics (radio active isotopes supervoltage x rays betatron etc) which it was believed might obviate some of the limitations and resultant complications inherent in the medium voltage range These newer modalities may in time prove superior but at present medium voltage x ray therapy is still the most efficacious method of treating most neoplasms by roentgen radiation

It requires a nicety of dosage planning to effect the maximum damage to the tumor associated with the maximum beneficial change of the normal contiguous tissues (with minimum damage to the tumor bed) Paterson has listed some of the local factors responsible for the selective differential that permits the utilization of x rays to destroy tumors

For tumor	*For normal tissue*
1 Size of tumor	1 Area or volume of tissue irradiated
2 Rate of growth of the tumor (predominantly mitotic activity)	2 Regenerative powers centers of growth
3 Depth and location of the tumor	3 Depth and location of tissue or organ
4 The bed of the tumor including vascularity extent of fibrous tissue bone or cartilage involvement	4 Vascularity presence of cartilage bone
5 Circumscription or invasion of the tumor	5 Functional status of tissue or organ
6 Microscopic diagnosis and perhaps to some extent the degree of differentiation	6 Degree of differentiation of tissue (embryonic adult etc)

There is thus, a definite differential range by which a given dose of irradiation will destroy cancer cells and not irreparably damage the tumor bed This differential depends upon the inherent sensitivity of tumors (lymphosarcoma very sensitive, melanoma very resistant) and the condition of the contiguous tissue bed i e a healthy well vascularized tissue bed will not be damaged by the ionizing radiations to the extent that an infected or avascularized tumor bed will be Even under ideal conditions the differential response between neoplastic and normal tissues is not very great

Computing Dose of Irradiation Delivered to Tumor

Since the effects of irradiation upon neoplastic processes depend upon the amount of ionizing radiation delivered to and absorbed by the tumor it is necessary to measure the quantity of radiation delivered from the machine to the air (D) thence to the skin (D) through a variable amount of subcutaneous tissues to the tumor (D)

As noted in Figure 17 1 there is very little margin of safety between tumor lethal dose of many malignant tumors and the tolerance or dose that can be safely administered to the skin without producing irreparable damage

The two factors that influence whether a given amount of irradiation is cancericidal and tolerated by the organism are (1) the total dose administered, and (2) the time necessary to deliver that dose If it is considered that a tumor dose of 6,000 r will destroy a given tumor, it is necessary to administer the dose over a long time interval (fractionation, pro-

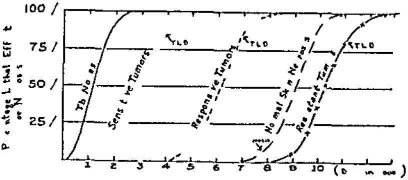


Fig 17 1 Possible expression of the relationship between x ray dosage and lethal effect on Tb nodes sensitive tumors responsive tumors normal skins and resistant tumors

TB nodes Tuberculous nodes added to show the dosage range to obtain a favorable response in chronic inflammatory tissue *TLD* is tumor lethal dose *Sensitive tumors* e g lymphosarcoma or seminoma: dose administered in 2 to 3 weeks *Responsive Tumors* e g (small or medium size) dose administered in 32 days *Normal skin* reaction with moderate-sized portal This spectographic representation of physical dosage range is not intended to portray exact limits and doses used in treatment but rather to give a sense of the order of magnitude of the dose-response ratio of several types of tumors and normal skin (*From* Paterson [68])

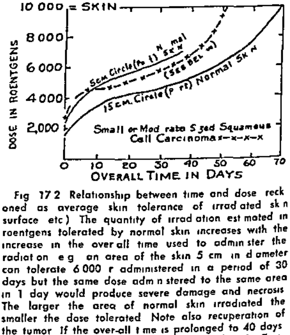


Fig 17 2 Relationship between time and dose reckoned as average skin tolerance of irradiated skin surface etc) The quantity of irradiation estimated in roentgens tolerated by normal skin increases with the increase in the over all time used to administer the radiation e g an area of the skin 5 cm in diameter can tolerate 6 000 r administered in a period of 30 days but the same dose administered to the same area in 1 day would produce severe damage and necrosis The larger the area of normal skin irradiated the smaller the dose tolerated Note also recuperation of the tumor If the over-all time is prolonged to 40 days then the total dose necessary to produce lethal effects in the tumor should be at least 7 000 r for a small sized squamous cell carcinoma Obviously administration of this dose in a shorter time is also lethal to the tumor but may produce necrosis in adjacent normal tissue (*From* Paterson [68])

TABLE 17 1 —TISSUE DOSE IN ROENTGENS CORRESPONDING TO A FREE AIR DOSE OF 100 ROENTGENS AT 50 CM FOCUS-SKIN DISTANCE

Depth (cm)	*Open Port*				*Cover on treatment cone ⅛ inch Bakelite*				*Cover on treatment cone ¼ inch Bakelite*			
	Irradiated area (sq cm)				*Irradiated area (sq cm)*				*Irradiated area (sq cm)*			
	5	*25*	*100*	*400*	*5*	*25*	*100*	*400*	*5*	*25*	*100*	*400*
	120 kv peak no filter H V L 1 0 mm Al or 0 035 mm Cu											
0	111	117	124	128	111	118	126	130	112	118	127	132
1	62	71	81	87	68	78	87	94	73	80	93	99
3	29	37	47	55	33	42	52	59	37	45	56	63
5	16	21	28	35	19	24	33	39	20	25	36	42
7	9	12	19	24	11	14	21	27	12	15	23	30
10	4	6	10	15	6	7	11	18	7	8	13	21
	150 kv peak 5 mm Al filter H V L 0 3 mm Cu											
0	115	125	136	150	115	126	138	154	116	127	140	159
1	93	114	131	148	93	113	131	151	94	110	130	151
3	61	83	105	126	61	78	101	123	61	77	98	123
5	39	56	76	98	39	55	74	96	39	53	73	95
7	25	39	56	75	25	38	55	74	25	37	53	75
10	14	22	35	52	14	21	34	51	14	22	34	51
12	8	15	26	41	8	13	26	39	8	14	25	40
	200 kv peak 0 5 mm Cu filter H V L 0 9 mm Cu											
0	114	124	136	149	114	125	138	153	115	126	141	158
1	95	115	133	150	95	114	132	150	94	111	133	152
3	63	87	109	131	63	84	105	129	63	82	103	128
5	43	61	82	107	43	60	77	104	43	58	77	103
7	29	43	63	85	29	42	61	83	29	42	59	82
10	17	26	41	61	17	25	40	58	17	25	39	58
12	13	20	33	50	13	18	30	48	12	18	30	48
15	6	11	22	33	6	10	21	32	6	10	21	32
20	3	5	11	15	3	5	11	15	3	5	11	16
	200 kv peak 2 0 mm Cu filter H V L 1 8 mm Cu											
0	109	117	126	136	109	117	127	138	110	118	128	139
1	90	109	124	137	91	107	122	137	91	106	120	135
3	61	82	102	121	62	80	90	117	63	77	96	114
5	42	60	79	101	42	59	76	97	42	57	74	93
7	28	43	60	80	28	42	58	79	29	41	57	75
10	17	27	43	60	17	26	41	58	19	26	40	57
12	13	20	34	50	13	19	33	48	13	19	32	47
15	7	13	24	34	7	12	24	34	7	12	23	35
20	3	6	11	19	3	6	11	18	3	6	11	18

Source O Glasser, E H Quimby, L S Taylor and J L Weatherwax *Physical Foundations of Radiology* [illegible] New York Paul B Hoeber Inc 19[illegible] (Courtesy of the authors and publisher)

traction) to take advantage of the destructiveness of the rays to the cancer cells during their different mitotic activities and yet permit regeneration of the surrounding normal tissues (Figure 17 2)

PHYSICAL FACTORS OF IRRADIATION

The physical factors (some of which may also alter the quality of the x ray beams) largely responsible for the quantity of x rays delivered to the skin and the underlying tissues are (1) kilovoltage (2) filtration (3) target skin distance (T S D) (4) size of portal (5) depth of tumor below the surface of the skin

1 *Kilovoltage (Table 17 1)* As the kilovoltage is increased from 120 to 200 kv there is an increase in the percentage depth dose delivered at various distances below the skin

2 *Filtration (Table 17 1)* As the filtration increases there is a relative increase in the percentage of depth dose delivered in comparison to the skin dose To increase the percentage depth dose by increasing filtration or target skin distance it is necessary to increase the time of administration to obtain a given number of roentgens (r) (See Table 17 3)

3 *Size of Portal (Table 17 1)* As the size of the portal increases there is an increase in the dose of roentgens both on the skin and in the tissues at various depths for the same dose (e g 100 r in air), owing to scatter of the primary x ray beam in all directions

4 *Depth Below Skin Surface (Table 17 1)* As the depth below the skin surface increases there is a decrease in the percentage dose delivered at various levels

5 *Target Skin Distance or Focus-Skin Distance (Table 17 2)* As the target skin distance increases the percentage of dose delivered at various depths below the skin increases

Medium voltage x ray units are flexible to a degree that full advantage can be made of each of the above factors and by their manipulation the most desired beam for a particular tumor can be obtained

Tumor Sensitivity and Tumor Curability

There is no direct relationship between radiation sensitivity and curability of tumors The size of the tumors is very important for

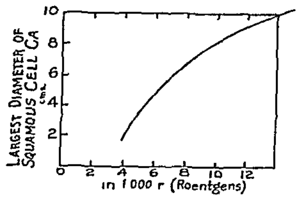


Fig 17 3 Possible relationship of lethal effect of x ray dosage and gross size of tumor As the diameter of the squamous-cell carcinoma increases the dosage in roentgens necessary to produce a lethal effect in the tumor increases Note that when the lesion is above 6 cm in diameter the dosage necessary to produce lethal effect in the tumor is such that it would cause necrosis in the adjacent normal tissues (see Table 17 5) (From Paterson [68])

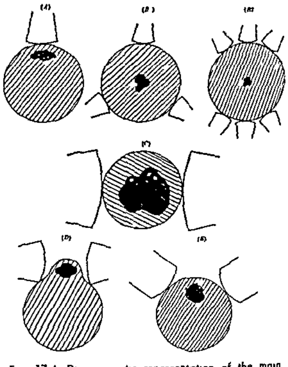


Fig 17-4 Diagrammatic representation of the main x ray field arrangements A Single field Multiple fields B1 and B2 Cross fire C Paired opposing D Tangent fields E Paired oblique by passing
Space between applicator ends and skin may be filled up with bolus or material that will allow for a more uniform spread of the irradiation in the tissues The solid black portion represents the tumor the lined section the normal tissue and the cylindrical figures the size and position of the x ray cones or applicators on the skin (From Paterson [68])

TABLE 17.2.—Factors for Determining Depth Doses at Various Focus Skin Distances in Terms of Each Depth Dose for 50 cm Distance as 100 Per Cent
(Skin dose 100 per cent for every distance)

Depth (cm)	*Focus Skin Distance in Centimeters*									
	15	*20*	*25*	*30*	*40*	*50*	*60*	*70*	*80*	*100*
	Percentage of Depth Dose at 50 cm									
0	100	100	100	100	100	100	100	100	100	100
1	91.5	94.4	96.0	97.4	99.4	100	101	101	101	102
2	84.1	89.3	92.8	95.0	98.1	100	101	102	103	104
3	78.1	85.0	89.4	92.7	97.5	100	102	103	104	106
4	72.5	81.0	86.8	90.6	96.6	100	102	104	106	108
5	68.2	77.4	84.0	88.7	95.9	100	103	105	107	109
6	64.0	74.2	81.5	87.0	94.7	100	104	106	108	112
7	60.5	71.3	79.2	85.1	94.0	100	104	107	110	114
8	57.1	68.5	77.2	83.8	93.4	100	105	108	111	115
9	54.5	66.2	75.2	82.3	92.7	100	105	109	112	117
10	51.8	64.0	73.5	80.9	92.1	100	106	110	114	119
11	49.6	61.8	71.7	79.8	91.6	100	106	111	115	121
12	47.5	60.0	70.2	78.4	90.9	100	107	112	116	123
15	42.3	55.2	65.9	75.3	89.6	100	108	115	120	127
17	39.4	52.4	63.5	73.0	88.7	100	109	117	122	131
20	36.0	19.0	60.5	70.5	87.0	100	110	120	125	136

Note The table gives factors only and not the actual percentage This table can only be used in conjunction with depth dose table

Source O Glasser E H Quimby L S Taylor and J L Weatherwax *Physical Foundations of Radiology* 2nd ed New York Paul B Hoeber Inc 19[illegible] (*Courtesy* the authors and publisher)

TABLE 17.3.—Effect of Variation in Filter on Depth Dose
(200 kv (peak) 100 sq cm Field 50 cm F S D)

Depth (cm)	*A—Number of r at depth per 100 r on surface*				*B—Number of r at depth per 100 r in air*			
	Filter (mm Cu)				*Filter (mm Cu)*			
	0.5	*1.0*	*2.0*	*4.0*	*0.5*	*1.0*	*2.0*	*4.0*
	r per 100 r on surface				*r per 100 r in air*			
0	100	100	100	100	136	132	126	120
2	89	89	90	92	121	118	113	111
5	60	61	63	65	82	80	79	79
7	46	47	48	50	63	61	60	59
10	30	32	34	37	41	42	43	44
15	16	17	19	20	22	22	23	24
Relative times of delivery of same number of roentgens	0.74	1.14	2.2	4.8	1.0	1.5	2.8	5.8

Source O Glasser E H Quimby L S Taylor and J L Weatherwax *Physical Foundations of Radiology* 2nd ed New York Paul B Hoeber Inc 195[illegible] (*Courtesy* the authors and publisher)

TABLE 17 1—STANDARDIZATION REPORT DOCTOR BRAESTRUP'S CALIBRATION REPORT
(Note the decrease in dose of r/min delivered as the FSD increased from 50 to 70 cm)

STANDARDIZATION REPORT

N Y Medical College
Flower and Fifth Ave Hospital
Fifth Ave at 105th Street
New York, N Y

H on V Generator Westinghouse 250 FVJP Tube Enclosure Protective X-Ray Tube Westinghouse

CONTR SETTINGS				KV	MA	FILTER			FSD	TIME TO DELIVER						HVL	r/min
										75 r		100 r		125 r		mmCu	in air
VTO		MA	VOLTS			Sn mm	Cu mm	Al mm	cm	min	sec	min	sec	min	sec		
23-20		1	6 0	250	15		1/2	1	47.3	0	42	0	57	1	11	1.6	106
									50	0	41	0	55	1	8		110
									60	0	59	1	18	1	38		76.5
									70	1	20	1	47	2	14		56 2
							1	1	47.3	0	57	1	15	1	34	2 3	79 5
									50	0	55	1	13	1	32		82 0
									60	1	19	1	45	2	12		57 0
									70	1	48	2	23	2	59		41 8
							COMPOSITE		47.3	1	9	1	32	1	55	2 8	65 2
									50	1	8	1	30	1	53		66 4
									60	1	38	2	10	2	36		46 1
									70	2	13	2	58	3	42		35 8
A	B	C	D	E	F	G	H	I	J	K		L		M		N	O

Inherent filtration of x-ray tube and its housing equivalent to approx. 0.15 mm Cu

The unit r refers to the international roentgen, the value of which has been obtained thru the calibration of instrument No. U-1

UBBraestrup

as they increase in size larger doses of irradiation must be administered to destroy them (Figure 17 3) but conversely as larger volumes of normal tissue are irradiated its tolerance diminishes (Table 17 5)

Radiation Portals (Figure 17-4)

In irradiating a tumor the following approaches for delivering the irradiation to the tumor may be used (medium voltage irradiation lends itself well to these technics)

1 *Single field or port* is used when the location of the neoplasm is such that only one approach is possible e g in certain skin cancers

2 *Multiple fields* are indicated for tumors so located that multiple or several portals of entry or beams can be converged to pass through the tumor from different external sites on the skin

The advantages are that the total dose to the tumor can be much greater enhancing the chances of obtaining tumor lethal dose There is less damage to the normal structures comprising each portal

The disadvantages include the extreme ac

TABLE 17 5 —SKIN TOLERANCE DOSES
(In roentgens)

Nominal time	Real over all time is just over	Field group	Small		Medium	Large	Regional
		Area (sq cm)	20 to 40	40 to 60	75 to 125	150 to 200	300 to 400
		Applicator sizes (in cm)	5 6½	7½	10 12 12½	15	20
		No of exposures	6×4 7×5 10×4	6×8 10×5 15×4	15×5 10×8 10×12	10×15 10×20 7½×20	20×15 20×20
1 day	2 hours	1	2 100	1 900	1 700	1 500	—
4 days	3 days	4	3 700	3 400	2 900	2 500	—
8 days	7 days	8	4 700	4 300	3 800	3 300	2 700
2 weeks	11 days	10*	5 100	4 700	4 100	3 600	3 000
3 weeks	18 days	15*	5 500	5 100	4 500	4 000	3 400
5 weeks	32 days	25*	6 300	5 900	5 300	4 800	4 300
10 weeks	67 days	50*	—	—	10 000	9 000	—

* Except Saturdays and Sundays (course of treatment starting on a Monday)

NOTE The tolerance decreases as the size of area is increased Therefore doses greater than the tolerance doses are very likely to produce necrosis As the over all time of administration of the dose (or fractionation) increases the normal skin can tolerate larger doses because there is some recuperation or recovery of the tissues after every irradiation Despite some recovery and reversibility of the damage caused by irradiation there are other irreversible reactions that are not immediately apparent but that eventually limit the amount of radiation that can be delivered The bottom row may be considered as the limit of this tolerance

SOURCE R Paterson Treatment of Malignant Disease by Radium and X Rays London Edward Arnold & Co 1948 p 38

TABLE 17 6 —HALF VALUE LAYER OBTAINED BY VARIATION IN VOLTAGE AND FILTRATION

Kilovolts	Filters	Half value layer
200	0 5 mm copper (Cu) 1 mm aluminum (Al)	1 mm Cu
	1 mm Cu 1 mm Al	1 7 mm Cu
	2 mm Cu 1 mm Al	2 mm Cu
250	Thoraeus filter (Composite filter)	
	0 44 mm Tin (Sn) 0 25 mm Cu 1 0 mm Al	2 8 mm Cu

TABLE 17 7

Depth Dose H V L 1 0 mm Cu (Approximately 200 kv 0.5 mm Cu filter) Roentgens at depth per 100 r in air					
Area Sq Cm (Diam Cm)	*20 (5)*	*50 (8)*	*100 (11 3)*	*225 (17)*	*400 (22 5)*
Air Dose	*100*	*100*	*100*	*100*	*100*
Depth Cm	*40 cm distance*				
0	122	130	136	144	149
1	111	124	132	142	149
2	97	110	120	133	140
3	84	96	106	121	128
4	67	79	91	105	115
5	55	69	77	93	102
6	46	59	68	82	89
7	39	50	58	71	79
8	33	43	52	63	72
9	27	35	44	55	61
10	23	30	38	47	56
11	20	26	33	42	46
12	17	22	28	36	40
15	11	16	21	28	30
17	7	9	14	19	21
20	5	6	9	14	17
	50 cm distance				
0	122	130	136	144	149
1	112	125	133	144	150
2	99	112	122	134	143
3	86	99	109	124	131
4	70	83	95	110	119
5	57	72	82	97	107
6	49	61	72	86	95
7	42	53	63	76	85
8	37	46	56	68	76
9	29	38	48	59	66
10	24	33	41	51	61
11	21	27	35	45	51
12	18	25	31	40	45
15	12	18	24	31	34
17	8	10	15	20	22
20	5	8	11	16	19

Depth Dose H V L 2 0 mm Cu (Approximately 200 kv 2 0 mm Cu filter) Roentgens at depth per 100 r in air					
Area Sq Cm (Diam Cm)	*20 (5)*	*50 (8)*	*100 (11.3)*	*225 (17)*	*400 (22.5)*
Air Dose	*100*	*100*	*100*	*100*	*100*
Depth Cm	*40 cm distance*				
0	116	121	126	132	136
1	105	115	123	131	136
2	92	103	111	120	128
3	76	88	98	109	118
4	65	75	86	98	106
5	54	65	76	87	97
6	46	56	66	78	84
7	38	47	57	68	75
8	32	41	49	59	67
9	28	35	44	54	60
10	24	31	39	48	54
11	21	28	35	45	49
12	19	24	31	40	44
15	12	16	21	28	31
17	9	12	16	21	23
20	5	7	10	14	17
	50 cm distance				
0	116	121	126	132	136
1	107	116	124	132	137
2	94	104	113	126	136
3	80	91	102	112	121
4	67	79	90	102	111
5	58	69	79	92	101
6	49	59	69	82	90
7	42	51	60	72	80
8	35	44	53	65	72
9	31	39	48	58	65
10	27	34	43	52	60
11	23	30	38	47	53
12	21	27	34	44	48
15	13	18	24	30	34
17	10	13	19	24	27
20	6	8	11	16	19

Gives the quality of the x ray beam (H V L) voltage and filter and the depth dose in percentage of 100 r in air at 40 and 50 cm T S D for various sizes of ports The first row 0 is the surface or skin dose Note that the surface dose is larger than the air dose owing to backscatter of the primary beam Also the surface dose increases with an increase in the size of the port The doses at various depths in cm below the surface are also given as percentage of the 100 r (air) dose

E g H V L 1 0 mm Cu
Area 20 cm port
T S D 40 cm
Depth 10 cm
} Dose 23 r for every 100 r in air administered

In this manner the tumor dose and the skin dose may be calculated if the total amount of r in air administered is known as well as quality of beam size of port, T S D and depth of tumor

SOURCE O Glasser E H Quimby L S Taylor and J L Weatherwax. *Physical Foundations of Radiology* 2nd ed New York Paul B Hoeber Inc 1952 (*Courtesy* the authors and publishers)

TABLE 17 8 —ILLUSTRATES THREE MAIN METHODS OF PRESCRIPTION

	Applicators	Fields	Given dose	Tumor dose: Per cent contributed to tumor	Tumor dose: Tumor dose	Skin dose: Per cent contributed from other fields	Skin dose: Total
1 Cancer of fauces							
3 field to T D	Rt post lat		4 930	51	6 000	Max 16	5 700
6 000 r in 5 weeks	Lt post lat		4 930	37		Max 10	4 930
	Submental ant	6×5 cm at 40	4 930	34		Nil	5 400
				122			
2 Nasopharynx growth with nodes							
2 large opposing fields to max skin dose 3 000 r in 8 days	Rt lat	10×15 at 50 cm	2 560	each 49	2 500	17	each 3 000
	Lt lat		2 560				
3 Abdominal radiation baths							
3 field	Ant oblique rt	35×25 cm at 80 dist	Each 40 r/day increasing 10 r/day to Max 100 r		140		145
Time indefinite	Ant oblique lt						
	Posterior	35 at 80 dist					

With the help of Figure 17 5 and Table 17 7 for example the tumor and skin doses above can be calculated In prescribing for x ray therapy the total dose and over all time are planned first and the specific details of administration then calculated knowing the size of tumor depth etc

Source R. Paterson *Treatment of Malignant Disease by Radium and X Rays* London Edward Arnold & Co 1948 p 9

curacy required to focus the radiation beams on tumor Owing to the possibility of x ray beams converging in regions outside the tumor hot spots may develop i e regions of severe damage to normal tissue or cold spots (ineffective doses) in certain portions of the tumor

Half Value Layer

The quality of an x ray beam is expressed by the term half value layer (H V L.) The more penetrating the beam the higher will be its designated half value layer Table 17 6 illustrates certain common filters and voltages used in medium voltage therapy and the corresponding half value layer of the beam

Depth dose and isodose charts obtained from experiments performed on phantoms simulating the conditions in the human body (see Table 17 7 and Figure 17 5) are available and the most satisfactory beam for a given situation can be chosen Table 17 8 demonstrates the method of manipulating the different physical factors to obtain the most efficient beam delivered to tumors of different anatomic sites The variations of technic necessitated by the type of tumor and the anatomic sites are evident Figures 17 6 17 7 and 17 8 present in detail the radiation programs developed to treat most effectively different cancers located at different depths within the body and located in tissues of different densities

GRID TECHNIC

Since it is difficult in some cases to deliver cancericidal doses with the conventional medium volt x ray therapy to deep seated tumors without irreparably injuring the overlying normal tissue investigators have tried various methods to increase the depth dose without exceeding the tolerance of normal tissues Of the many modifications attempted the "grid" appears to be the most promising This is a device consisting of a screening substance such as lead rubber which has multiple open

TABLE 17 7

Depth Dose
H V L 1 0 mm Cu
(Approximately 200 kv 0.5 mm Cu filter)
Roentgens at depth per 100 r in air

Area Sq Cm (Diam Cm)	*20 (5)*	*50 (8)*	*100 (11.3)*	*225 (17)*	*400 (22.5)*
Air Dose	*100*	*100*	*100*	*100*	*100*
Depth Cm		*40 cm distance*			
0	122	130	136	144	149
1	111	124	132	142	149
2	97	110	120	133	140
3	84	96	106	121	128
4	67	79	91	105	115
5	55	69	77	93	102
6	46	59	68	82	89
7	39	50	58	71	79
8	33	43	52	63	72
9	27	35	44	55	61
10	23	30	38	47	56
11	20	26	33	42	46
12	17	22	28	36	40
15	11	16	21	28	30
17	7	9	14	19	21
20	5	6	9	14	17
		50 cm distance			
0	122	130	136	144	149
1	112	125	133	144	150
2	99	112	122	134	143
3	86	99	109	124	131
4	70	83	95	110	119
5	57	72	82	97	107
6	49	61	72	86	95
7	42	53	63	76	85
8	37	46	56	68	76
9	29	38	48	59	66
10	24	33	41	51	61
11	21	27	35	45	51
12	18	25	31	40	45
15	12	18	24	31	34
17	8	10	15	20	22
20	5	8	11	16	19

Depth Dose
H V L 2 0 mm Cu
(Approximately 200 kv 2 0 mm Cu filter)
Roentgens at depth per 100 r in air

Area Sq Cm (Diam Cm)	*20 (5)*	*50 (8)*	*100 (11.3)*	*225 (17)*	*400 (22.5)*
Air Dose	*100*	*100*	*100*	*100*	*100*
Depth Cm		*40 cm distance*			
0	116	121	126	132	136
1	105	115	123	131	136
2	92	103	111	120	128
3	76	88	98	109	118
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5	54	65	76	87	97
6	46	56	66	78	84
7	38	47	57	68	75
8	32	41	49	59	67
9	28	35	44	54	60
10	24	31	39	48	54
11	21	28	35	45	49
12	19	24	31	40	44
15	12	16	21	28	31
17	9	12	16	21	23
20	5	7	10	14	17
		50 cm distance			
0	116	121	126	132	136
1	107	116	124	132	137
2	94	104	113	126	136
3	80	91	102	112	121
4	67	79	90	102	111
5	58	69	79	92	101
6	49	59	69	82	90
7	42	51	60	72	80
8	35	44	53	65	72
9	31	39	48	58	65
10	27	34	43	52	60
11	23	30	38	47	53
12	21	27	34	44	48
15	13	18	24	30	34
17	10	13	19	24	27
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$\left.\begin{array}{l}\text{E g H V L 1 0 mm Cu} \\ \text{Area 20 cm port} \\ \text{T S D 40 cm} \\ \text{Depth 10 cm}\end{array}\right\}$ Dose 23 r for every 100 r in air administered

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6 000 r in 5 weeks	Lt post lat		4 930	37		Max 10	4 930
	Submental ant	6×5 cm at 40	4 930	34		Nil	5 400
2 Nasopharynx growth with nodes				122			
2 large opposing fields to max skin dose 3 000 r in 8 days	Rt lat Lt lat	10×15 at 50 cm	2 560 2 560	each 49	2 500	17	each 3 000
3 Abdominal radiation baths 3 field Time indefinite	Ant oblique rt Ant oblique lt Posterior	35×25 cm at 80 dist 35 at 80 dist	Each 40 r/day increasing 10 r/day to Max 100 r		140		145

With the help of Figure 17 5 and Table 17 7 for example the tumor and skin doses above can be calculated In prescribing for x ray therapy the total dose and over all time are planned first and the specific details of administration then calculated knowing the size of tumor depth etc

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curacy required to focus the radiation beams on tumor Owing to the possibility of x ray beams converging in regions outside the tumor hot spots may develop i e regions of severe damage to normal tissue or cold spots (ineffective doses) in certain portions of the tumor

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GRID TECHNIC

Since it is difficult in some cases to deliver cancericidal doses with the conventional medium volt x ray therapy to deep seated tumors without irreparably injuring the overlying normal tissue investigators have tried various methods to increase the depth dose without exceeding the tolerance of normal tissues Of the many modifications attempted the grid appears to be the most promising This is a device consisting of a screening substance such as lead rubber which has multiple open

ings arranged in an orderly checkerboard fashion (Figure 17 9) The intact segments of the screen protect islands of normal tissue from the primary beam These islands of normal tissue then act as centers of regeneration for subsequent recovery of the irradiated tissues Kohler in 1909 first attempted this technic by placing a steel wire mesh on the skin of animals administering massive doses which he called fractionation of the x ray dosage in space In 1933 Liberson reported the use of what he called a multiple perforated lead screen and investigated its physical and biologic effects

Marks recently suggested the use of a lead rubber grid that partly eliminates secondary irradiation from the lead Clinical reports on the application of the grid technic by Harris Jolles and Marks have shown encouraging results Harris was impressed by the degree of palliation afforded to the patients and tolerance of the normal tissue for the very large doses of x ray used He has treated deep seated tumors using opposite fields and occasionally a third lateral field and delivered a maximum of 18 000 r in air per port protracting the treatments over a period of 35-45 days Note that this is more than four times the maximal dosage usually administered per port by the conventional methods of medium x ray therapy He warns against Marks method of using 24 000 r per port in air in 28 days because of the deleterious effects on the skin and underlying tissue

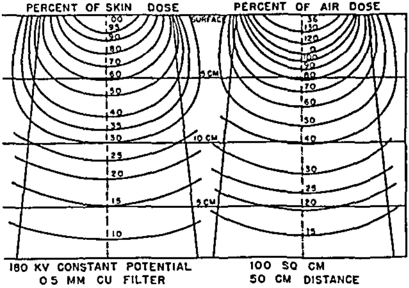


Fig 17 5 Isodose charts 180 kv constant potential 0.5 mm Cu filter 0 9 mm Cu h v l 100 sq cm field 50 cm focus skin distance Isodose (or same dose) levels are expressed as percentage of skin or air dose The air dose in the left hand graph would be approximately 77 r Note that the central axis of the beam indicated by interrupted lines(— — —) shows the greatest dose at each depth level and that the dosage decreases as the distance from the central axis increases Note also that although the applicator limits to some extent the volume of tissue irradiated (indicated by the oblique lines ╱╲) the amount of irradiation spraying the adjacent normal tissues as a result of scattering of the primary beam may be considerable not only on the skin but especially in the depth of tissues This scattering increases with the increase in size of ports (From Glasser Quimby Taylor and Weatherwax [25])

One of the main disadvantages attributed to the use of the grids is the inhomogeinity of the x ray dosage throughout the tumor bed However it appears from the measurements of Loevinger and of Cohen and Palazzo that with an increase in depth to 10 cm the hills *and valleys in the isodose* curves flatten out because of the relatively increased scatter of the primary beam Another disadvantage described by Jacobson and Lipman is that the depth doses at 10 cm with the grid are approximately 50 per cent that of the con

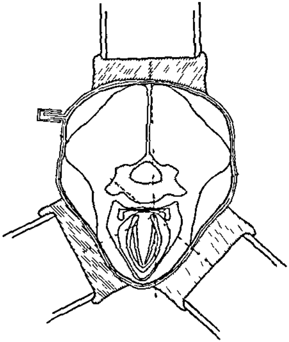


Fig 17 6 Carcinoma of larynx extrinsic (arytenoid) Three field beam directed x ray treatment with midrose (or plaster of Paris) and wax collar

Desired dosage

Tumor dose of 5 500 r in 5 weeks
Equal given doses on each field

CALCULATION Not on balanced dose basis

1 *Tumor Dosage*

Field	*Applicator*	*Tumor depth*	*Per cent D D*	
Right anterior oblique	7 × 5 cm	5 0 cm	54 2	= 143 7 per cent
Left anterior oblique	7 × 5 cm	4.5 cm	58 5	
Posterior	7 × 5 cm	9 0 cm	31 0	

143 7 / = 5 500 r   100 /o = 3 830 r

From applicator end

2 *Skin dosage*

Field	*Applicator*	*Direct † Skin per cent D D*	*Per cent D D from other fields*	*Total skin dose*
Right anterior oblique	7 × 5 cm	90	34 + 18	5 440
Left anterior oblique	7 × 5 cm	90	32 + 18	5 360
Posterior	7 × 5 cm	90	2 + 2	3 600

† Allowance made for 1 3 cm wax between applicator and skin

Given dose on each field = 3 830 r
Maximum skin dose = 5 440 r
Tumor dose = 5 500 r

Shows portals used and calculation of tumor and skin dose Note posterior port is not frequently used because of the direct irradiation of the spinal cord and relatively small dose delivered to the tumor site (From Paterson [68])

ventional method (see Table 17 9) However the advantage of this technic is in the ability of skin areas protected by the grid to recover thus enabling the tissues to be exposed to unusually high doses of irradiation The grid technic also permits the utilization of fewer portals to obtain adequate lethal doses for deep seated tumors especially when multiple portals are impractical It has also been stated that the grid method is easier to use and in some cases even less burdensome to patients who would otherwise receive tedious rotational or multiple port therapy

Harris uses the following factors

Kv	*H V L*	*T S D*	*Portal size*
200	0 9 mm Cu	40	40-400 cm
400	4 1 mm Cu	70	50 225 cm

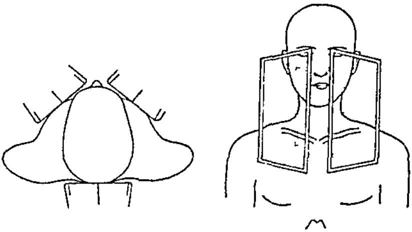


Fig 17 7 Lymphosarcoma of nasopharynx (limited lymph node involvement) Radical regional x ray therapy Three 25 × 12 5 cm rectangular felds at 60 cm F S D; two anterior and one posterior

Desired dose

Tumor dose 3 500 r Maximum skin dose 3 500 r in 3 weeks

CALCULATION

1 *Tumor dosage*

Field	*Applicator*	*Tumor depth*	*Per cent D.D*	
Right anterior	25 × 12.5	10 5 cm	40	= 126 per cent
Left anterior	25 × 12.5	10 5 cm	40	
Posterior	25 × 12.5	9 0 cm	46	
	126 per cent = 3 500 r	100 per cent = 2 780 r		

2 *Skin dosage*

Field	*Contribution from other field*	*Given dose*	*Total dose*
Right anterior	13 + 8 = 21	2 780	3,360
Left anterior	13 + 8 = 21	2 780	3 360
Posterior	13 + 13 = 26	2 780	3 500

Tumor dose = 3 500 r
Maximum skin dose = 3 500 r

D D depth dose 2 780 r given skin dose per port necessary to obtain depth dose of 3,500 r Contribution from other field results from overlapping to some extent of exit and entrance beam as well as to the scattering of the primary beam and this is in percentage (determined from depth dose and isodose charts) Since the dose to be administered per port is 2 780 r to the skin and the total duration of the treatment is 3 weeks each port must receive approximately 500 r skin dose per treatment (*From* Paterson [68])

Open areas of grid 40 per cent of portal area

Grid openings 1 to 1 5 cm in diameter

Daily dose 600 1 200 r (air)

Over all treatment time 28-45 days

Total doses 12 000 to 24 000 r (air) per portal

For flat surfaces a grid with holes of 1 cm is used

On irregular surfaces e g axillary and inguinal nodes holes are 1 5 cm in size

In our experience this method has been especially useful in the treatment of cancer of the lung and bladder In cases of cancer of the lung we have tried a combined form using the grid device and usual open port with medium volt x ray therapy and obtained encouraging results The following factors were employed

Two opposite fields (10 by 15 cm) with the grid

12 000 r (air) were given to each portal 3 500 r (air) was also given through a lateral conventional open port

220 kv 50 T S D Thoreaus filter

Open area of the grid was 50 per cent of the portal area (10 by 15 cm)

Grid openings 1 cm in diameter

Daily dose 500 1 000 r (air) for grid ports

Over all treatment time 30-45 days

With this combined method we have accomplished the twofold purpose of exposing the

TABLE 17 9.—TABLE OF DEPTH DOSE WITH GRID FOR 100 r MEASURED IN AIR FOR DIFFERENT SIZES OF FIELDS

(a) under opening (b) under covered portion (c) average
T S D 50 cm H V L 0 94 mm Cu

Depth in cm	*Area of field in sq cm* 50	100	150	200	300	400
	(a) Under opening					
0	112	113	115	116	123	125
1	97 3	99 5	101 3	103 8	109 5	111 5
2	83 0	86 3	88 2	92 0	96 5	98 7
3	70 3	74 3	76 8	80 5	84 3	86 5
4	60 0	64 0	67 0	70 0	73 5	75 5
5	51 0	55 0	58 0	60 8	64 3	66 5
6	43 5	47 3	50 7	53 0	55 8	57 8
7	36 5	40 3	43 7	45 5	48 2	50 0
8	30 3	34 0	37 3	39 2	41 3	43 0
9	24 8	28 3	31 5	33 0	35 0	36 7
10	20 0	23 2	26 2	27 7	29 3	31 0
15	8 0	10 2	11 6	12 5	13 8	15 0
	(b) Under covered portion					
0	16 5	18 5	21 5	23 0	23 3	25 0
1	19 0	21 0	23 8	25 5	26 5	28 2
2	20 3	22 3	25 3	27 5	28 7	30 7
3	20 5	22 8	26 0	28 7	30 0	32 5
4	19 5	22 7	25 8	29 0	30 3	33 0
5	18 2	22 0	25 2	27 7	29 5	32 7
6	16 5	20 5	24 0	26 3	28 5	31 5
7	14 5	18 7	22 2	24 5	26 7	30 0
8	12 5	16 5	20 0	22 0	24 5	27 5
9	10 6	14 5	17 7	19 3	22 0	25 0
10	9 0	12 5	15 7	17 0	19 3	22 0
15	4 0	6 0	8 0	8 8	10 0	11 8
	(c) Average					
0	54 3	56 0	59 0	60 3	63 0	65 0
1	50 3	52 5	55 8	57 5	60 0	62 0
2	45 8	48 5	52 5	54 2	56 5	58 8
3	41 0	44 3	48 5	50 5	52 7	55 0
4	36 0	39 7	44 0	46 3	48 5	50 8
5	31 0	35 0	39 0	41 3	43 8	46 2
6	26 7	30 7	34 5	36 8	39 0	41 3
7	23 0	26 8	30 3	32 5	34 5	36 8
8	19 3	23 3	26 7	28 5	30 5	32 5
9	16 2	20 0	23 5	24 7	27 0	28 7
10	13 3	17 2	20 2	21 5	23 5	25 2
15	5 5	7 7	9 4	10 4	11 5	13 0

Depth dose chart of grid device Open area of grid was 40 per cent Compare with Table 17 7 which is a depth dose chart with conventional open port. Other technical factors are approximately the same Note that for a portal area of 100 sq cm the dose at 10 cm depth for conventional port is 41 per cent whereas the average dose at 10 cm is only 1[illegible] per cent with grid (Courtesy J I Jacobson and A Lipman)

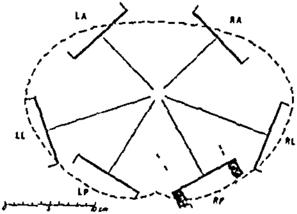


Fig 17 8 Radical x ray treatment for bladder cancer Schematic diagram shows field distribution (one field shows thickness of applicator walls) Desired dose 6 000 r 5 weeks Fields 6 × 8 cm

Prescription

Field	*Given dose*	*Tumor dist (with compression)*	*Per cent D D*	*Tumor contribution*
RA	4 100	9	32	1,312
LA	4 100	9	32	1 312
RP	3 240	10.5	25	810
LP	3 240	10.5	25	810
RL	5 000	13	18	900
LL	5 000	13	18	900

Total Tumor Dose—6 044

LA left anterior field RA right anterior field LL and RL left lateral and right lateral fields LP and RP left posterior and right posterior fields (From Paterson [68])

skin to a milder reaction (12 000 r (air)—grid method usually produces moderately severe yet tolerable skin reaction—Figure 17 10) and obtaining an effective tumoricidal dose (6 000 6 500 r at 10 cm depth) We have preferred the utilization of the conventional open port on the lateral field because of the technical difficulty of properly keeping the grid on the lateral aspect of the chest

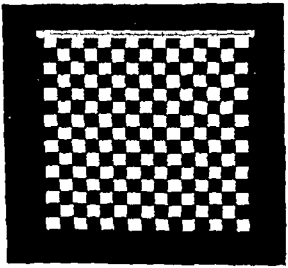


Fig 17 9 A photograph of the lead rubber grid 15 × 15 cm in size showing checkerboard configuration The white areas are open squares The total open area is 50 per cent of the portal area

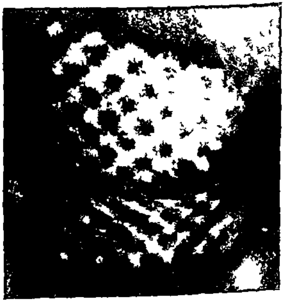


Fig 17 10 This is a photograph showing the skin reaction on the chest of a patient at the end of 3 weeks after the administration of 10 000 r in air (to this port) Note checkerboard configuration Technical factors 220 kv T S D 50 cm Thoraeus filter Open area of grid was 50 per cent of total area (10 × 15 cm) Grid openings 1 cm in diameter

ADVANTAGES OF MEDIUM VOLTAGE THERAPY OVER OTHER FORMS OF X RADIATION

Flexibility By altering the kilovoltage filtration and target skin distance a tumor situated either superficially or within the depths of the body can be treated Practically any tumor situated anywhere in the average sized individual can receive a cancericidal dose of ionizing radiations generated by a medium voltage x ray unit

Protection of adjacent structures A 2 mm sheet of lead or lead rubber over such vital structures as the eyes and testes will protect these structures from administered irradiation and permits the utilization of irregularly shaped ports Many medium voltage x ray units have built in lead diaphragms and lighted localizers that permit visual adjustment of the size shape and direction of the radiation beam

The *skin reaction* that accompanies medium voltage therapy may be considered an advantage rather than a disadvantage By limiting the total dose and fractionating it so that serious damage to the skin does not occur vital internal structures are protected

The *exit dose* is usually negligible except for certain anatomic locations as the neck so that the cross fire technic is permitted

The *universality of medium voltage* irradiation has permitted mass production of equipment which places the price range at a level where this equipment can be afforded by almost any hospital and many individual therapists

The over all salvage ratio of patients treated by medium voltages is similar to that obtained by the higher voltage

DISADVANTAGES OF MEDIUM VOLTAGE X RAY THERAPY

The rapid fall in depth dose renders accurate measurements of the quantity and *quality of the irradiation at a distance difficult* and for certain tumors necessitates delicate adjustment of cross firing technics to assure adequate irradiation and its proper distribution so that certain portions of the tumor may not be underexposed and other portions over exposed (hot spots) by the irradiation

The relatively small size of the portals permitted by this type of irradiation usually necessitates the utilization of multiple adjacent *ports This necessitates additional treatment* periods and increases the risk of over or underexposure of the borders of the adjacent portals

The relatively high amount of backscatter produces a disproportional amount of radiations delivered to the skin and to the tissues at variable depths from the skin from that measured in air This necessitates additional computations in determining surface and depth dosages This rapid falling off produces a rather heterogeneous beam because of the

TABLE 17 10—TUMORS OF TONSILLAR REGION RESULTS WITH ROENTGEN THERAPY

Author and type of treatment	*Carcinoma*			*Lymphosarcoma apparently localized to tonsillar region*		
	Number of patients	*5 year survival*		*Number of patients*	*5 year survival*	
		Number of patients	*Per cent*		*Number of patients*	*Per cent*
Coutard (External irradiation)	65	21	30			
Martin and Sugarbaker (External and peroral irradiation interstitial irradiation of nodes)	92	15	15			
Berven				49	17	35
del Regato				37	15	40
Total	157	36	20–25	86	32	35–40

TABLE 17.11.—TUMORS OF BASE OF TONGUE TREATED WITH X RAY

Author	*Epidermoid carcinoma*			*Lymphosarcoma apparently localized*			*Epidermoid cancer of valleculae and free portion of epiglottis*		
	Number of patients	*5 year survival*		*Number of patients*	*5 year survival*		*Number of patients*	*5 year survival*	
		Number of patients	*Per cent*		*Number of patients*	*Per cent*		*Number of patients*	*Per cent*
Baclesse	127	7	5				102	16	15
del Regato				12	4	33			

TABLE 17.12.—MALIGNANT NASOPHARYNGEAL TUMORS TREATED WITH X RAY

Author	*Carcinoma*			*Lymphoepithelioma*			*Lymphosarcoma*			*All groups*		
	Number of patients	*5 year survival*		*Number of patients*	*5 year survival*		*Number of patients*	*Cure or 5 year survival*		*Number of patients*	*5 year survival*	
		Number of patients	*Per cent*		*Number of patients*	*Per cent*		*Number of patients*	*Per cent*		*Number of patients*	*Per cent*
Baclesse and Dulac	30	4	10–15							102	16	15
Nielsen	11	4	35									
Lenz				17	6	35	10	5	50			
Nielsen				15	4	25	10	3	30			
Godtfredsen										266	59	22
Total	41	8	20	32	10	30	20	8	40	368	75	20

TABLE 17.13.—MALIGNANT HYPOPHARYNGEAL TUMORS. RESULTS OF TREATMENT

Author	*Radical surgical treatment*			*Roentgen treatment*		
	Number of patients	*5 year survival*		*Number of patients*	*5 year survival*	
		Number of patients	*Per cent*		*Number of patients*	*Per cent*
Graham	15	2	15			
Coutard [15]				200	23	10
Jacobsson				322		
Upper hypopharynx						10
Lower hypopharynx						15
Total				522		10–15

TABLE 17 14 —LARYNGEAL CARCINOMA RESULTS OF TREATMENT

Author	Early cases						Moderately advanced cases			Advanced cases		
	Operation			X ray therapy			X ray therapy			X ray therapy		
		5 year survival			5 year survival			5 year survival			5 year survival	
	Number of patients	Number of patients	Per cent	Number of patients	Number of patients	Per cent	Number of patients	Number of patients	Per cent	Number of patients	Number of patients	Per cent
Ackerman [1c] and del Regato							Total laryngectomy results variable but seem to be about 50 per cent 5 year survival					
Jackson Partial laryngectomy	74	41	55–75									
Lenz [52]				10	8	80	17	8	50	21	4	20
Coutard [14]										142	39	27
Desjardins *et al*										139	12	10
Harris *et al*				42	27	65						
Blady			80–85	81		70–75						
Total			75	133		70				302	55	15–20

INTERPRETATION Shimkin in his compilation of a number of untreated patients with cancer of the larynx finds the mean duration of life from the apparent on et of disease to be approximately 1 months None of the patients survived for 5 years after the onset of the cancer It is apparent from the above studies that x ray therapy i therefore of definite value X ray treatment gives practically the same prognosis for survival as does surgical resection Many of the advanced ca es were undoubtedly inoperable Furthermore x ray treatment does not necessarily prejudice the ul equent use of surgery when deemed advisable

TABLE 17 15 —THYROID CANCER RESULTS OF TREATMENT

Author	Type of treatment	No of patients	5 year survival		10 year survival		15 year survival		Total cases			
									Operable cases		Advanced cases	
			No of patients	Per cent	No of patients	Per cent	No of patients	Per cent	No of patients	5 year survival per cent	No of patients	5 year survival per cent
Guzman	Advanced cases incomplete surgical removal with x ray treatment	23		25							23	25
Graham and McWhirter	Complete or subtotal surgical excision with x ray treatment	29		70–75					29	70–75		
	Inoperable (no distant metastasis) palliative x ray treatment	37		15							37	15
	Inoperable adequate x ray *treatment*	39		30							39	30
Hare and Salzman	Alveolar adenoma with invasion surgical removal most received x ray treatment	49	38	75	19	35	7	10–15	49	75		
	Papillary *adenocystoma* surgery with x ray therapy if extension	48	31	60–65	23	45	13	20	48	65		
	Papillary adenocarcinoma same as above	38	30	75	20	50	7	15	38	75		
	Alveolar cancer surgery with x ray treatment	24	7	25–30	5	20	1	5			24	25–30
	Small cell cancer surgery with x ray treatment	30	6	20	2	5					30	20
	Giant cell cancer surgery with x ray treatment	9	2	25							9	25
Total									164	65–70	163	20–25

INTERPRETATION In the early or localized cases x ray therapy following surgical removal appears to give good prognosis In advanced cases x ray treatment is primarily palliative It must be noted that some cancers of the thyroid have a slow evolution therefore the value of x ray therapy is difficult to evaluate.

TABLE 17 16 —ESOPHAGEAL CANCER TREATMENT WITH X RAY

Engelstad		Rolf Kohler	
	5 year survival		
242 patients	3* (1 to 2 per cent)	296 patients	
	1	Average survival after beginning of treatment 8 months	
		Per cent patients dead	Interval of life from time of treatment
* Only 1 case proved histologically		22	3 months
		50	6 months
		81	1 year
		3	2 years
		2	5 years

INTERPRETATION Shimkin collected approximately 300 cases of untreated esophageal cancer in which the mean duration of life from apparent onset was 12 months Very few patients were alive years after the apparent onset Both surgery and radiation therapy offer little better prognosis However the palliation effect from x ray therapy is very helpful

large numbers of secondary electrons produced and the range of these secondary electrons is fairly short

The limited depth of penetration limits its use for deep seated tumors in large men and extremely fat women

Bone absorbs a large amount of the irradiation from medium voltage x ray This produces damage to the marrow with resultant pancytopenia favors the production of late fractures and limits the dosages aimed at tumors behind bones

ROENTGEN THERAPY FOR SPECIFIC MALIGNANT NEOPLASMS

Methods of treating specific neoplasms are presented in detail throughout these volumes hence are omitted from this chapter The results obtained by the use of medium voltage x radiation either alone or in conjunction with other treatment methods will serve to summate the applicability of this type of irradiation in the treatment of cancer End results obtained by means of medium voltage x radiation are also presented and discussed in detail throughout these volumes

TABLE 17 17 —BRONCHOGENIC CARCINOMA RESULTS OF TREATMENT

Author	*Surgery*									*X ray treatment*			*Control cases*	
	Total number patients studied	*Exploratory thoracotomy*		*Pneumonectomy or lobectomy*		** to 5 yrs*		*7 to 10 yrs*			*year survival*		*No cases without treatment*	*Total survival life expectancy*
		No pts	*Per cent*	*No pts*	*Per cent*	*No pts*	*Per cent*	*No pts*	*Per cent*	*No pts*	*No pts*	*Per cent*		
Edwards	1 016	103	10	70	5–10	13	1	5	less than 1					
Leddy										(inoperable) 125	5	4	125	Less 1 year after diagnosis
Moersch and Tinney quoted by Leddy [49]													315	14 months

INTERPRETATION Neither surgery nor x ray therapy offers good results in most cases of bronchogenic carcinoma. However the palliative results of x ray therapy are often very satisfactory

TABLE 17 18 —BREAST CANCER RESULTS OF TREATMENT

Clinic	No. of cases	Stage I Per cent of 5 year survival: Rad mast & P O rad	Rad mast only	Simple mast & P O rad	Stage II Per cent of 5 year survival: Rad mast & P O rad	Rad mast only	Simple mast & P O rad	Stage III Per cent of 5 year survival: Surgery & P O rad	Surgery only	Radiation only	Stage IV Per cent of 5 year survival: Radiation only
Westminster (Cade)	348		87		Preop rad 29					20	0
Presbyterian N Y (Haagensen)	435		71 8		Stages II and III surgery only 39 6 percent						10
Royal Infirmary (McWhirter)	1345			89			44	Simple mast 29			Palliation only
Radiumhemmet (Nohrman)	767	73 1			44 8						
Middlesex London (Windeyer)	917		62 7		34 7			28			8
Univ of Minnesota (Stone)	209	57			39						
Mass Genl Hosp (Taylor)	395		78		Stages II and III radical mastectomy P O radiation in some cases 34 per cent						
Hartford Hospital (Wells)	350		49 2		Stages II and III radical mastectomy P O radiation in some cases 24 per cent						
Lack and Livingston			70			23–25					

R M = radical mastectomy
P O rad = postoperative radiation therapy

TABLE 17 19 —RESULTS OF CONVENTIONAL AND SPECIAL RADIOTHERAPEUTIC PROCEDURES IN CERVICAL CARCINOMA

Method	*Author*	*Year*	*5 year survival rate per cent*
Radium alone	Heyman Sweden	1914–31	21 6 absolute
Radium and x rays	Heyman Sweden	1932–41	39 9 absolute
Radium alone	Dresser Mass	1924–28	25 0 absolute
Radium 200 kv x rays	Dresser Mass	1934–38	46 0 absolute
Radium alone	Hunt free cases	1931–36	20 5 absolute
Radium and x rays	Hunt free cases	1937–41	42 1 absolute
Radium and x rays	Hunt private cases	1932–44	66 7 absolute
800 kv x rays and radium	Schmitz	1948	43 4 relative
Transvaginal and external x irradiation	Caulk	1949	35 0 absolute
Interstitial radium and x rays	Waterman	1947	44 4 relative

From Hunt [38] This table compiled by Hunt shows that better results are obtained with integration of radium and roentgen therapy Note that there is no significant difference in results obtained with conventional x ray and supervoltage x ray therapy

TABLE 17 20 —MALIGNANT TUMORS OF TESTIS RESULTS OF TREATMENT (ORCHIECTOMY AND POSTOPERATIVE X IRRADIATION)

	Seminoma			*Adenocarcinoma and malignant mixed tumor*		*All groups 5 year survival*		*All groups*	
Author	*5 year survival without metastasis per cent*	*All groups Number of patients*	*5 year survival per cent*	*Number of patients*	*5 year survival per cent*	*With metastasis per cent*	*Without metastasis per cent*	*Total number of patients*	*5 year survival per cent*
Ahlbom	80		65		35		70	119	50
O Connell and Geschickter		75	60	74	10–20			149	35–40
Leucutia *et al*						30	80	110	55
Total			60–65		20		75	378	45–50

INTERPRETATION Prognosis for seminoma with no clinically detectable metastasis treated by orchiectomy and postoperative abdominal x irradiation to full tolerance do e is very good For the other forms of malignant tumor the results are much less favorable

TABLE 17 21 —MALIGNANT OVARIAN TUMORS RESULTS OF TREATMENT

Author	Surgery + x irradiation: Group I, Primary tumor removed no metastasis		Group II, Tumor and metastasis completely removed		Group III, Local metastasis partly removed		Group IV, Inoperable		Surgery + x irradiation Total			
	Number of patients	5 year survival per cent	Number of patients	5 year survival per cent	Number of patients	5 year survival per cent	Number of patients	5 year survival per cent	Number of patients	5 year survival per cent	10 year survival per cent	15 year survival per cent
Kerr and Elkins									165	30 (absolute)		
Freed and Pendergrass	21	71	12	50	32	25	19	21	84	40		
Allan and Hertig									85	45	35	15
Total									334	35–40		

INTERPRETATION Postoperative irradiation appears to be of value in most cases In inoperable cases x irradiation helps although prognosis is poor

TABLE 17 22.—RESULTS OF X RAY TREATMENT

	Lymphoid Tumors								*Endothelioma of Ewing*	
	Lymphosarcoma						*Total Cases*			
	Localized site		*Two clinical sites*		*Three clinical sites*		*Lymphosarcoma and Hodgkins*			
Author	*Number of patients*	*5 year survival per cent*	*Number of patients*	*5 year survival per cent*	*Number of patients*	*5 year survival per cent*	*Number of patients*	*5 year survival per cent*	*Number of patients*	*5 year survival per cent*
Lenz	37	55	70	25	135	10	242	20		
Hare *et al*							181	20–30		
Coley *et al*									73	<5

INTERPRETATION X ray therapy is of definite value for the localized form of lymphoid tumors Shimkin in a collected series of untreated lymphoblastoma (163 cases) found 10 per cent of the patients alive 5 years after apparent onset of the disease

TABLE 17 23.—INTRACRANIAL AND ORBITAL TUMORS RESULTS OF TREATMENT

	Medulloblastoma Cerebelli Surgery and roentgen treatment		*Bilateral Retinoblastoma Surgical removal of eye with more advanced lesion + roentgen treatment of other*	
Author	*Number of patients*	*5 year survival per cent*	*Number treated and traced*	*5 year survival per cent*
Ingraham *et al*	56	5		
Reese *et al*			19	6 vision 20/200 6 blind no recurrence Total 60 per cent

INTERPRETATION 1 Medulloblastoma has poor prognosis even with combination of surgery and roentgen therapy However Ingraham shows average survival improves with increase of total dosage of x ray administered

Total dose x ray given (includes all ports and repeated series)	*Number of patients*	*Average survival in months after first treatment*
a less than 4 000 r	9	8 months
b 4 000 10 000 r	15	31 months
c 10 000 30 000 r	9	54 months

Therefore x ray therapy is indicated to limits of tolerance

Retinoblastoma even in bilateral cases shows surprisingly good prognosis as to life and to a lesser extent to function

TABLE 17.24.—PITUITARY TUMORS

Author	Type	X ray therapy: Number of patients	X ray therapy, Response: Excellent per cent	X ray therapy, Response: Good per cent	X ray therapy, Response: No change or poor per cent	Surgical treatment: Number of patients	Surgical treatment: Good results per cent	Surgery and postoperative irradiation: Number of patients	Surgery and postoperative irradiation: Free of recurrence 5 year survival per cent
Kerr	Eosinophil	11	Similar response						
	Chromophobe	37							
	Others	2							
	Total	50	58	12	30				
Evans *et al*						40	55 to 60	31	80
Ellis	Eosinophil	47	30	25	45				
Bachman & Harris	Eosinophil	21		40					
	Chromophobe	35	50 to 60						
	Basophil	5		80					
Buschke						*Davidoff's series*		*Surgery clinical arrest per cent*	
						Eosinophil		40	
						Chromophobe		60	
						Operative mortality		6–13	

INTERPRETATION. For pituitary tumors x ray therapy offers as good if not better results than surgical resection. However, nonresistive tumors are often cystic and in these cases excision may be of great help.

TABLE 17.25. CARCINOMA OF CORPUS UTERI. RESULTS OF TREATMENT

Author	Surgical methods only: Stage I 5 year survival per cent	Surgical methods only: Stage II 5 year survival per cent	Surgical methods only: Stage III 5 year survival per cent	Surgical methods only: Operative mortality per cent	Surgical methods only: Total patients	Surgical methods only: Average 5 year survival per cent	Radium plus operation: Number of patients	Radium plus operation: 5 year survival per cent	Operation plus postoperative x irradiation: Number of patients	Operation plus postoperative x irradiation: 5 year survival per cent	X irradiation plus operation: Number of patients	X irradiation plus operation: 5 year survival per cent
Harnett	75	45	35	5	74	50	12	75	22	65		
Miller and Henderson											96	75

INTERPRETATION. The best prognosis seems to be offered by the use of radium followed by surgical excision. Surgical excision alone is least effective.

CHAPTER 18

The Clinical Application of Supervoltage X-Ray Therapy (1,000–3,000 Kv) in Cancer Treatment

Ralph Phillips

A change in wavelength alters not only the penetration absorption and scattering of the x ray beam but also the nature and spatial distribution of the absorbed energy In the supervoltage range of 500 to 5 000 kv absorption is mainly by the Compton process which depends directly upon electronic density and is almost independent of atomic number whereas in the low and medium voltage range below 400 kv (where photoelectric absorption predominates) and in the megavoltage range from 5,000 kv upward (where pair production is the main mechanism), absorption shows a close dependence on atomic number If clinical results depended only on the physical dose of radiation absorbed in a tumor physical considerations could predict the therapeutic value of different wavelengths In the twenty five years since the first supervoltage x ray treatment was administered much clinical knowledge of its value has been accumulated but the variables in x ray therapy are so numerous—dose wavelength fractionation dosage rate over all time the powers of adaptability change and recovery inherent in living cells the nature of the cancer and the nature of the patient—that no final answer as to the wave length dependence of clinical results is yet available

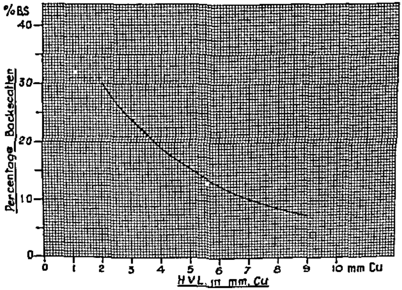


Fig 18 1 Variation of percentage backscatter with quality of x ray beam expressed as half value layer in copper (100 sq cm field 100 cm F S D) (From R Phillips [15] Courtesy H K Lewis & Co Ltd)

ADVANTAGES OF SUPERVOLTAGE THERAPY

Increased Skin Tolerance

The backscatter of superhard x rays is only about one third that of medium hard x rays so that equal doses in air of the two qualities are very different doses on the skin (Figure 18 1) Above 3 000 kv the percentage back

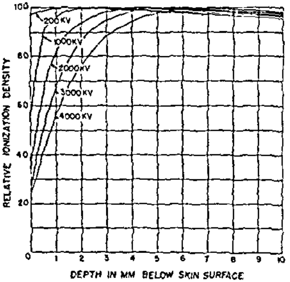


Fig 18 2 Distribution of ionization in the first 10 mm below the skin for 200 kv and for supervoltage roentgen rays with various filters (100 sq cm field 100 cm F S D) (From Trump [22] courtesy Radiology)

scatter is independent of area and amounts to 5 per cent or less However even when measured with backscatter the skin reaction produced by equal doses is less from super voltage than from medium voltage radiation For equal skin reactions the skin dose at 1 000 kv is about 50 per cent greater than at 200 kv the threshold erythema dose is 1 000 r at 1 000 kv compared with 680 r at 200 kv (Quimby [5] Trump [22]), and the second degree erythema dose is 1 500 r at 1 000 kv for 100 sq cm field compared with 1 000 r at 200 kv (Table 18 1) The absence of photo electric absorption by the sulfur in the skin the forward direction of the Compton elec trons with the build up of the maximum ioni zation at depths of 1 mm or more (Figure 18 2) and the smaller biologic efficiency of the high speed electrons in the surface layers all combine to produce this increased skin tolerance for superhard radiation but the skin must of course be left uncovered for this advantage to be fully realized

With the usual fractionation technic the skin reaction appears more slowly takes longer to reach its maximum and remains drier with supervoltage than with medium voltage x rays It is generally possible to give the desired tumor dose without producing a moist erythema and at 3 000 kv often with only a threshold erythema [3]

The late effects of skin atrophy and telan giectasia are not appreciably different after supervoltage from the similar effects of me dium voltage radiation but there is often more subcutaneous induration and fibrosis so that a second full course of supervoltage therapy is generally inadvisable Most parts of the skin will tolerate two or even three full courses of medium voltage irradiation but further ir radiation after previous supervoltage therapy is very liable to result in late radionecrosis [8]

TABLE 18 1 —Variation of Skin Erythema Dose with Quality of Radiation

Kv	*H V L mm*	*Skin area sq cm*	*Degree of erythema*	*Skin dose r*
100	1 0 Al	70	1	270
200	0 9 Cu	70	1	680
250	1 5 Cu	100	2	1 000
300	3 3 Cu	6	1	1 200
700	7 0 Cu	70	1	800
700	7 6 Cu	5	1	1 400
1 000	10 0 Cu	6	2	1 800
1 000	3 8 Pb	70	1	1 000
1 000	3 1 Pb	100	2	1,500
1 000	7 0 Pb	100	1	1 000
2 000	10 0 Pb	100	1	1 800
3 000	12 5 Pb	100	1	2 250

[illegible]

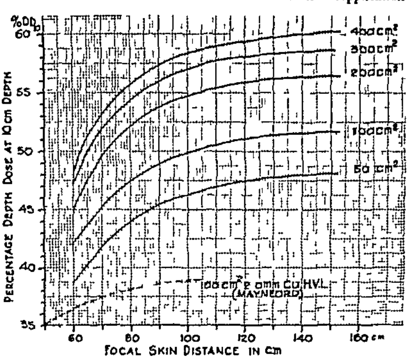


Fig 18-3 Variation of percentage depth dose at 10 cm depth with F S D for various field areas (1 000 kv H V L 9 mm Cu) (From R Phillips [15] courtesy H K Lewis & Co Ltd)

Increased Depth Dose

The gain in percentage depth dose with superhard over medium hard x rays is shown in Table 18 2 and Figures 18 3 and 18-4 and is greatest for small areas With supervoltage it is unnecessary to use large fields in order to get an adequate depth dose so that the body is spared unwanted irradiation with consequent reduction in systemic effects

Increased Systemic Tolerance

Owing to reduced scattering, the supervoltage x ray beam maintains its geometric shape through the tissues the total energy

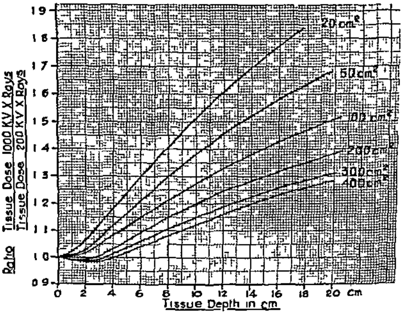


Fig 18-4 Tissue dose at 1 000 kv H V L 9 mm Cu compared with that at 200 kv H V L 2 mm Cu for the same skin dose at various depths and field areas (100 cm F S D) (From R Phillips [15], courtesy H K Lewis & Co Ltd)

TABLE 18 2 —VARIATION OF PERCENTAGE DEPTH DOSE WITH QUALITY OF X RAY BEAM
(100 cm focus skin distance)

Field area	5 cm depth 250 kv	5 cm depth 1 000 kv	Gain per cent	10 cm depth 250 kv	10 cm depth 1 000 kv	Gain per cent
	P D D					
24 sq cm	56 5	71 0	26 7	27 5	42 5	54 5
100 sq cm	69 0	77 5	12 3	38 2	50 2	31 4
300 sq cm	76 0	81 6	7 4	46 6	55 4	18 9

Field area	15 cm depth 250 kv	15 cm depth 1 000 kv	Gain per cent	20 cm depth 250 kv	20 cm depth 1 000 kv	Gain per cent
	P D D					
24 sq cm	13 1	25 6	95 5	6 0	15 0	150 0
100 sq cm	20 0	30 0	50 0	10 7	18 1	69 1
300 sq cm	27 5	36 0	30 9	16 0	22 0	37 5

absorbed in the body for a given tumor dose is thus much less for superhard radiation and hence systemic effects such as radiation sickness or leukopenia are less frequent than with medium hard x ray therapy

More Homogeneous Dose Distribution

The absorption of medium hard x rays in bone is some two or three times greater than in soft tissues but it is only about 10 per cent greater for 1 000 kv radiation [19 21] There are two resulting advantages of supervoltage first there is less danger of radionecrosis of bony and cartilaginous structures traversed by the x ray beam such as the mandible in the treatment of intraoral cancer the thyroid cartilage in treating cancer of the larynx or the neck of the femur in treating pelvic cancer secondly the actual tissue dose in tumors lying deep to bony structures is not much less than the measured dose in phantoms of unit density material—practical examples where this is of importance are cancer of the maxilla cancer of the esophagus (especially a posterior field traversing the vertebrae) the apical axillary nodes lying behind the clavicle cancer of the rectum and cancer of the tonsil

There is also less variation in the ionization from point to point in the tissues with super hard than with medium hard radiation so that the absorbed energy is more uniformly distributed with a consequent greater probability of producing the desired biologic effect *Two factors contribute to this increased homogeneity of tissue dose* the supervoltage x ray beam undergoes much less degradation as it traverses the body than a 250 kv beam and the range of its secondary electrons i e the length of the ionization tracks is some four times longer

The specific ionization decreases as the quantum energy increases thus the mean number of ions per micron of tissue is 15 for 1 000 kv and 80 for 200 kv [6] The average length of an ionization track is about 140 μ at 1 000 kv and 30 μ at 200 kv [11] Many biologic experiments have shown that the effect varies directly as the specific ionization since 1 r of any quality radiation is by definition *the same number of ions hard x rays may* be found to be less efficient per roentgen than soft x rays in producing the type of biologic effect that is more or less independent of the spatial distribution of ions It would however be hazardous to apply such experimental findings to the clinical problem where large volumes of tissue are irradiated and where distribution of the energy absorbed both in space and in time is of importance

DISADVANTAGES OF SUPERVOLTAGE THERAPY

Size and Cost of Apparatus

The early x ray apparatus for 600 kv and upward was air insulated and hence of large size requiring much space (Figures 18 5 18 6) with correspondingly high capital outlay Modern apparatus is freon insulated under pressure and can be installed in treatment rooms of normal height (13 ft) (Figures 18 7 18 8) though a greater height is desirable for full flexibility The cost is still considerable ($70 000 minimum) but is offset to some extent by increased output since the efficiency of x ray production is proportional to approximately the third power of the voltage

Inflexibility

In the early apparatus some of which is still in use the tube was fixed the x ray beam was either vertical or horizontal and field sizes were limited by the difficulty of changing unwieldy diaphragms Thus the patient had to be adjusted to the apparatus instead of the x ray beam being freely and accurately adjustable to the patient Any improvement in clinical results from supervoltage might well be masked if comparison is made between an inflexible supervoltage apparatus and a fully flexible medium voltage apparatus

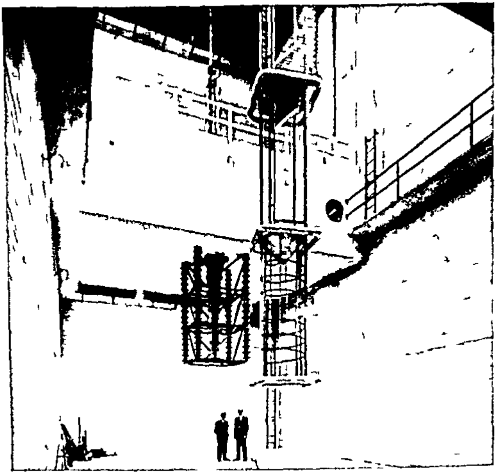


Fig 18 5 Lauritsen s x ray tubes circa 1930 California Inst tute of Technology

Diaphragms

With medium voltage radiation irregular field shapes are readily obtained by using pieces of 2 mm Pb or lead rubber on the patient and structures such as the eye or the testis can easily be shielded With million volt radiation an inch of lead is required to reduce the x ray intensity to 1 per cent of the main beam so that only rectangular fields can be obtained with a continuously adjustable diaphragm and various special devices of a more

or less cumbersome nature are necessary for the shielding of important structures or for obtaining circular oval and irregular field shapes Furthermore if the focal spot is large and the continuously adjustable diaphragm mounted nearer to the target than half the focal skin distance the resulting penumbra vitiates the advantage of the lack of side scatter from the main beam

Radiation Damage

With medium voltage radiation skin tolerance is generally the limiting factor in dosage and late radiation damage to structures other than the skin is therefore unlikely With supervoltage radiation skin reactions are no longer a trustworthy guide and late radiation damage to deeper structures is very likely to result if dosage is pushed to the apparent limits of immediate tolerance at the time of treatment In the irradiation of pelvic tumors both Mudd and Phillips [15] observed a late subcutaneous induration that produced gross edema of the lower limbs and marked limitation of movement at the hip joints In the irradiation of metastatic cancer in lumbar lymph nodes to a tumor dose of around 6 000 r in six weeks Friedman has found a number of late radiation injuries—gastric ulceration damage to the anterior horn cells with a flaccid paresis of the lower limbs and sarcoma of the spine and erector spinae muscles In

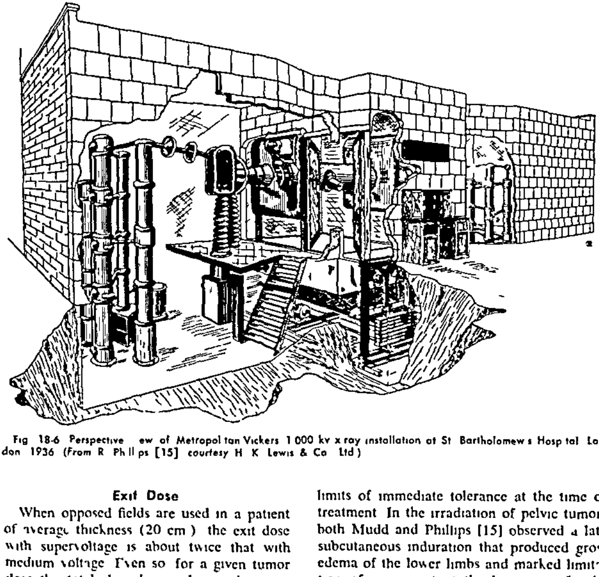


Fig 18-6 Perspective view of Metropolitan Vickers 1 000 kv x ray installation at St Bartholomew's Hospital London 1936 (From R Phillips [15] courtesy H K Lewis & Co Ltd)

Exit Dose

When opposed fields are used in a patient of average thickness (20 cm) the exit dose with supervoltage is about twice that with medium voltage Even so for a given tumor dose the total skin dose is less with supervoltage e g for a tumor dose of 4 000 r at 10 cm depth with two opposed 10 × 10 cm fields 20 cm apart the given skin dose at 1 000 kv H V L 10 mm Cu is 4 000 r and the maximum skin dose 4 800 r whereas at 250 kv H V L 2 mm Cu the given skin dose is 5 700 r and the maximum skin dose 6 200 r

the attempt to cure otherwise incurable cancer the risk of radiation injuries must be accepted in a small proportion of cases since knowledge of normal tissue tolerance dose levels is imperfect and there are individual extremes of

Fig 18 7 Memorial Hospital New York 1 000 kv treatment room 1947 General Electric apparatus

variability but the proportion of injuries can be kept to 1 or 2 per cent if careful attention is given not simply to skin dose or tumor dose but to the dose levels in all the tissues irradiated

GENERAL INDICATIONS FOR SUPERVOLTAGE X RAY THERAPY

If clinical results depend largely upon the physical dose of radiation absorbed in a tumor supervoltage x rays are to be preferred in the treatment of deep seated tumors of limited extent where multiple converging beams of small cross sectional area can be accurately directed to give a homogeneous high dose in the desired region a rapid fall-off of dose in the surrounding normal tissues and a minimal integral dose

Supervoltage radiation is also indicated whenever bone has to be traversed by the beam for two reasons the greater penetration gives a bigger and more accurately estimated tumor dose deep to the bone and the smaller energy absorption in the bone lessens the risk of late radionecrosis or of the interruption of bone growth in the case of children

Supervoltage therapy may be indicated in the treatment of tumors that have recurred after medium voltage therapy or in the later

Fig 18 8 Van de Graaff 2 000 kv Installation at Massachusetts Institute of Technology 1949 adapted by Dr J G Trump for rotation therapy (Courtesy *Radiology*)

treatment of disseminated disease (e g Hodgkin s) that has become refractory to medium voltage therapy It is also indicated in abnormally large individuals where the depth of the tumor would render medium voltage of little value In attempting the cure of disseminated radiosensitive tumors e g seminoma testis supervoltage therapy may be

preferable since theoretically there should be less damage to hemopoietic bone marrow

SUPERVOLTAGE THERAPY IN VARIOUS TYPES OF CANCER

Carcinoma of the Rectum

Carcinoma of the rectum is virtually incurable by medium voltage x rays Phillips [14] first reported the disappearance of the primary growth in about one third of the (mostly advanced) patients treated with supervoltage x rays to a tumor dose of 5 000 to 6 000 r in five to six weeks The technic of treatment and the isodose distribution compared with medium voltage irradiation are illustrated in Figure 18 9 Williams in a later independent

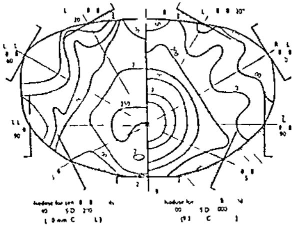


Fig 18 9 Isodose distribution on transverse section for the treatment of cancer of the rectum through 10 fields 18 × 8 cm by 200 kv H V L 2 mm Cu 40 cm F S D (left half) and by 1 000 kv H V L 9 mm Cu 100 cm F.S D (right half) (From R Phillips [15] courtesy H K Lewis & Co Ltd)

follow up of Phillips patients found that there were eight five year cures out of 127 inoperable patients treated during the years 1937 1944 there were also six five year cures in a group of patients with recurrent carcinoma after radical operations and a number of patients who died of senility or metastases in the liver without recurrence of the primary growth and often without requiring a colostomy Williams states that about 60 per cent of the patients treated obtained complete relief of symptoms and returned to their normal work

Williams reported four five year cures for anal cancer out of twelve advanced patients treated with million volt x rays the tumor dose being about 4,500 r in five weeks Anal cancer does not as a rule respond well to medium voltage x radiation

Carcinoma of the Breast

Irradiation of the breast and the three main lymph node drainage regions (axillary, supraclavicular and internal mammary) separately inevitably results in regions of underdosage and overdosage Levitt and Phillips in 1933 attempted to improve the two field Holfelder Finzi tangential technic by adding a third supraclavicular field that was directed from above downward and slightly medially and by including between the anterior and posterior tangential fields the whole arc of tissues superficial to a plane drawn from the posterior axillary line to the contralateral border of the sternum With medium voltage x rays (H V L 1 5 mm Cu) this technic can give a tumor dose of 3 000 to 3 500 r in four weeks and in advanced inoperable breast cancer resulted in an 18 per cent three year and a 9 per cent five year absolute survival rate But in large individuals or bulky tumors the dose was still not homogeneous and fell below the minimum of 3 000 r then considered necessary Supervoltage irradiation permits a tumor dose of 4 000 to 5 000 r insures homogeneous dosage in the patient of average size and even in the outsize individual whose cross sections are depicted in Figure 18 10 gives a reasonably satisfactory isodose distribution The results of supervoltage therapy show almost a threefold improvement over medium voltage in this group of advanced inoperable breast cancer the absolute five year survival rate being 25 per cent included in the survivors are two lactation carcinomas in patients aged twenty three and twenty six respectively In reporting the late follow up of these cases Williams states I can confirm Phillips observation that disappearance of the primary tumor and regional lymphatic metastases is more certainly and more easily obtained with supervoltage than with deep x ray therapy

Inevitably the majority of patients with advanced breast cancer die of distant metastases in the lungs liver and bones but the palliation afforded by healing or prevention of ulceration and fungation of the primary growth is entirely worth while (Figure 18 11)

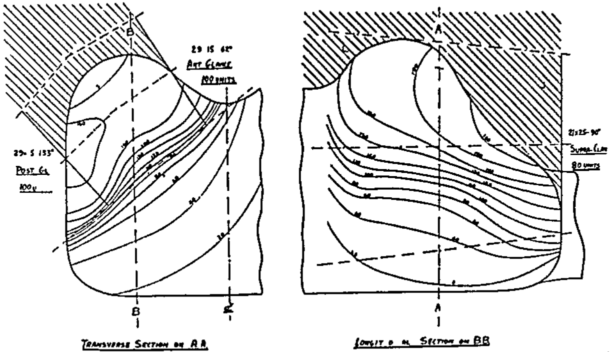


Fig 18 10 Isodose distribution on transverse and longitudinal sections for the treatment of cancer of the breast in a very large patient through three fields—anterior tangential 29 × 15 cm., posterior tangential 29 × 15 cm supraclavicular 21 × 25 cm (100 kv) Shading indicates packing with bolus (*From* R Phillips [15] *courtesy* H K Lewis & Co Ltd)

The combination of hormone and supervoltage therapy adds still more to this palliation and may further prolong the period of useful survival

Cancer of the Esophagus

Cancer of the esophagus has not so far given any better results with supervoltage than with medium voltage x ray therapy Cantril and Buschke have one cure out of twenty three patients treated to a tumor dose of 4,500 to 6 000 r in six to eight weeks and Williams has no survivors from forty two cases given an average tumor dose of 5 000 r in four weeks While some patients who die from perforation or pneumonia show no evi

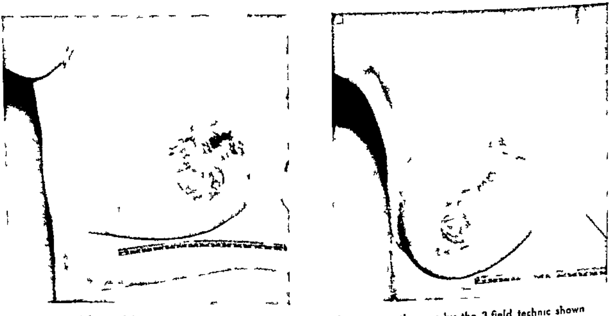


Fig 18 11 Advanced breast cancer before and after supervoltage x ray therapy by the 3 field technic shown in Figure 18 10

dence of carcinoma at postmortem and others die from hepatic or pulmonary metastases without evidence of local recurrence the majority die from persisting disease or from local recurrence after a short period of palliation

Cancer of the Lung

Bronchogenic carcinoma like cancer of the *esophagus has proved just as intractable to* supervoltage as to medium voltage x ray therapy half the treated patients die within six months and only 5 per cent survive longer than two years Watson and Urban state that a tumor dose of 3 500 r gave the maximum palliation (relief of hemoptysis cough dyspnea and atelectasis) but about 6 000 r gave the longest survival period The difficulty is that any worthwhile tumor dose (minimum 3 000 r) inevitably produces pulmonary fibrosis with symptoms sometimes as disabling and distressing as those of lung cancer for this reason the writer suggests that pneumonectomy should be done whenever possible even though some growth is left behind for such residual tumor can often be irradiated through small fields to a high dose level

Cancer of the Bladder

Supervoltage therapy gives better results in cancer of the bladder than medium voltage but even so the absolute five year cure rate is only 15 per cent [1 24] Most of the cures however are in the group of papillary carcinomas of which about 35 per cent survive five years free of cancer The successful dose time levels have been 4 000 to 6 000 r in four to eight weeks if these dose time levels are exceeded when the entire bladder has to be irradiated there is considerable risk of desquamation of the whole mucous membrane resulting in an irritable contracted bladder that necessitates a cystectomy

Cancer of the Prostate

Zuppinger showed that regression of the tumor with palliation of symptoms could be obtained if a sufficiently high tumor dose was given and Mudd in his pioneer investigation of supervoltage therapy reported 26 per cent of patients symptom free for periods up to four years

Cancer of the Uterus

The substitution of supervoltage for medium voltage x rays in the standard combined radium x ray treatment of cancer of the uterus has not so far given statistically better results The main uncertainty in the irradiation of any cancer primary in the pelvis is the extent and situation of the lymph node metastases If cancer is confined to the true pelvis telecobalt rotation therapy is technically the method of choice

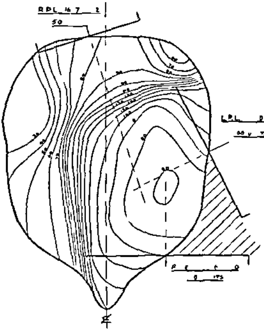


Fig 18 12 Isodose distribution on transverse section for the treatment of an advanced carcinoma of the maxillary antrum through three fields anterior 16 × 11 cm left posterolateral 16 × 10 cm right posterolateral 16 × 9 cm 1 000 kv Shading indicates bolus (From R Phillips [15] courtesy H K Lewis & Co Ltd)

Carcinoma of the Maxillary Antrum

In advanced carcinoma of the antrum the body walls are extensively invaded usually with perforation of the hard palate and the floor of the orbit and infiltration of the pterygoid fossa The greater penetration and homogeneity of supervoltage x rays apparently improved the cure rate from 12 per cent with 200 kv to 30 per cent with 1 000 kv in one series of cases but the small number of cases treated at 1 000 kv does not make this difference statistically significant Nearly all long term survivors develop an irradiation cataract since it is impossible adequately to irradiate

the disease in the floor of the orbit and at the same time protect the lens The average tumor dose in this series was 4,500 r in three to four weeks the field arrangement and isodose distribution in a patient who has survived eight years is illustrated in Figure 18 12 and the extensive nature of the disease can be judged from the large size of the fields that it was found necessary to employ

Pituitary Tumors

Cantril and Buschke [1] prefer supervoltage radiation for the treatment of pituitary tumors since advantage can be taken of the greater penetration, lessened scatter and negligible skin reaction they give a tumor dose of 4 000 r in five to six weeks with marked improvement in the visual fields in both eosinophil and chromophobe tumors

Intrinsic Carcinoma of the Larynx

In spite of the relatively superficial location of the tumor supervoltage therapy has some advantages over medium voltage in the treatment of carcinoma of the vocal cords absorption in the more or less ossified thyroid cartilage is less skin tolerance is higher and a unilateral tumor can be adequately irradiated through a single portal There is also some evidence of better results from harder radiation Lederman and Cade have found teleradium therapy and Williams supervoltage x ray therapy superior to medium voltage x ray therapy The recommended tumor dose is 5 000 to 7 000 r in four to six weeks

Cancer of the Testis

Friedman has demonstrated that the tumor lethal dose for malignant teratoma is often as high as 6 000 r in six to eight weeks There are of course many malignant testicular tumors particularly seminomas which have been cured by tumor doses of 2 000 to 3 000 r in three to four weeks and these can be successfully treated with medium voltage x rays A tumor dose of 4 500 r or more however can seldom be given to the abdominal aortic lymph node metastases unless supervoltage radiation is used this dose level carries a considerable risk of damage to the gastric mucous membrane and other normal tissues but is justifiable when inoperable metastases of teratomatous pathology are known to be present Friedman has obtained an 18 per cent five year survival rate in malignant teratoma testis with proved abdominal lymph node metastases and a 100 per cent five year survival rate in seminoma with metastases

THE PLACE OF SUPERVOLTAGE IN PRESENT DAY RADIOTHERAPY

The present position of supervoltage x ray therapy may be summarized in question and answer form

1 Does the quality of the radiation alter biologic response?

The answer is Yes' for, at any rate some biologic reactions if the unit of dose is the roentgen e g for bacteria and viruses [9] hard x rays are more lethal than soft x rays the skin erythema dose increases with increasing hardness Specific ionization varies with quality, and nearly all biophysicists accept specific ionization as an important factor in determining biologic response

2 Does the quality of the radiation alter tumor response?

The majority answer is No , e g Cantril and Buschke Williams Schulz and Holmes all subscribe to the view that the inherent nonresponsiveness of some cancers to ionizing radiation does not change if the quality of the radiation is changed nor do most tissues or organs tolerate any higher dosage of super hard x rays than of lower voltage x rays The minority regard the question as still unsettled

3 Do clinical radiotherapeutic results depend upon the quality of the radiation?

Opinions are fairly equally divided comparison of results between different institutions are useless because of the great variability of many factors other than quality The only fully controlled comparison was made by Wood between gamma rays and 200 kv x rays the respective cure rates in 214 patients were 28 per cent and 20 per cent a difference that is not statistically significant

In the brief period of sixty years the radiotherapy armamentarium has greatly expanded none of the early methods has been abandoned but only curtailed as each new method adds its own particular advantages and indications

Years	*X ray apparatus*	*Gamma ray apparatus*
1896–1956	Superficial therapy 50 140 kv	Radium 1 50 millicuries
1916–1956	Deep therapy 150 250 kv	Radium 1 10 curies
1930–1956	Supervoltage therapy 400 2 000 kv	
1950–1956	Megavoltage therapy 4 000 24 000 kv	Cobalt 50 2 000 curies

CHAPTER 19

The Clinical Application of Moving-Field Radiotherapy

Jens Nielsen

INTRODUCTION

This chapter presents a brief survey and evaluation of radiotherapy with a moving beam (moving field radiotherapy moving beam irradiation Bewegungsbestrahlung) of deep seated malignant tumors The three main forms—rotation irradiation pendulum or arc irradiation and convergent irradiation —are presented

GENERAL CONSIDERATIONS AND HISTORIC EVOLUTION OF MOVING FIELD RADIOTHERAPY

The principle of cross firing has made possible a certain elevation of the depth dose without exceeding the tolerance dose of the skin however, it has certain drawbacks The method of cross firing with many fields requires cumbersome and time consuming planning and technic of adjustment Even so it cannot avoid overlapping of adjoining beams This results in increased doses ("hot spots) in the healthy tissue below the surface and an uneven distribution of intensity within the tumor and surrounding area

The worst shortcoming however is that the tumor doses obtainable in this way are not sufficient to produce complete eradication of the tumor This is probably an important reason why irradiation of malignant tumors in deep seated organs has met with small success so far

Historic Development of Moving Beam Irradiation

It is interesting to note that very early in the history of radiotherapy the idea was proposed that the cross fire method with stationary fields might be replaced by a continuously moving field on the skin in order to avoid the drawbacks of cross firing (Kohl 1906 Pohl 1913) The introduction of this new principle gives a more complete and uniform utilization of the skin area at disposal to the entrance of the rays and an essential increase of the depth dose In addition unwanted dose increases due to overlapping of the beams in the depths are eliminated Moreover the depth dose is delivered exactly to the desired area at any distance below the skin It is fairly homogeneous throughout and shows a steep decline in the immediate surroundings about the tumor

A few reports on the clinical application of moving field therapy were published at the beginning of the century (Meyer, 1913) but it was neglected during World War I and the years following (Knox 1915) not to appear in the literature until 1929 (Archangelsky) In 1937 Dessauer called attention to the advantages of the method

Recently Dessauer Nakaidumi DuMesnil de Rochemont Nielsen Neumann and Wachsmann and others have developed the clinical application rotation irradiation turning the sitting patient about his own axis in the horizontal beam In contrast Kohler preferred the immovable lying down position making the tube swing as a pendulum about a horizontal axis pendulum or arc irradiation Finally Henschke Green and associates and Steed and associates have used Kohl s arrangement to produce convergent rays by using a round field and circular movements of the tube about an axis at right angles to the longitudinal axis of the patient This principle of con

vergent irradiation has been elaborated by Bischoff

ROTATION IRRADIATION

Principles and Practice

DEFINITION

Rotation irradiation is the simplest and most perspicuous form of moving field irradiation in which the tube turns in relation to the patient in a circular movement about an axis of rotation parallel to the axis of the body For technical reasons this relative movement of the tube is realized by rotating the patient who is sitting or standing on a platform 360° about a vertical axis through the center of the tumor at a horizontally incident central ray

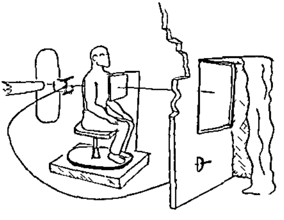


Fig 19 1 Sketch of primitive rotation equipment

TECHNIC

As a rule the patient sits on a motor driven rotating seat whose rate of rotation can be varied The rectangular beam is defined by means of an adjustable lead diaphragm attached to the tube head at a distance of about 20 cm from the focus The diaphragm may be opened or closed and moved from side to side (this generally being more convenient than moving the tube) or even tilted by remote control through Bowden cables By a simple mechanical contrivance the tube may also be moved up and down by remote control In a more elaborate construction the chair with the patient may be moved—also by remote control—by means of two small reversible direct current electromotors—in all directions This is of great help in the adjustment of the patient in order to get the axis of rotation exactly in the center of the tumor, and if constant fluoroscopic control is used during the rotation the necessary small adjustments of the patient during the rotation period are executed physically more correctly than by the side to side movements of the diaphragm Especially when using very narrow beams as in rotation therapy of the esophagus is fluoroscopic control advantageous

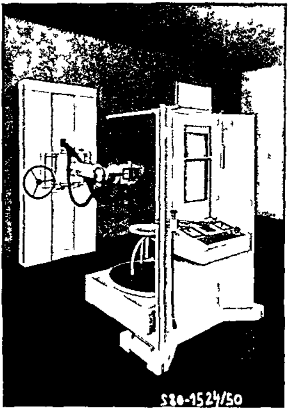


Fig 19 2 Ready made unit for rotation therapy with constant screening control of the treatment area (Courtesy Siemens)

Concerning further technical details it may be mentioned that irradiation corresponding to conventional deep roentgentherapy generated at 180 to 200 kv filtered through 0 5 mm Cu (H V L 1 mm Cu) at 10 to 20 ma will give a ray quality and an output suitable for rotation at a target skin distance of 50 to 60 cm within a reasonable radiation time (5 to 15 minutes)

DOSE DISTRIBUTION

It must be stressed that in rotation therapy the field of entry is of little importance The

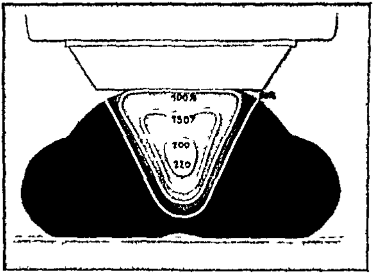


Fig 19-3 Dose distribution in a horizontal section of the chest in rotation irradiation of esophageal carcinoma (courtesy F Wachsmann)

simplest form of rotational irradiation of circular cylindrical bodies centric axial radiation with the central ray vertical on the axis of the cylinder corresponds roughly to rotation therapy of carcinoma of the esophagus It has been shown by experimental measurements on phantoms and anatomic preparations that a dose distribution is obtained in the central plane that takes the form of a bell shaped curve The maximum intensity represented by a nearly homogeneously irradiated plateau around the axis of rotation, corresponds approximately to the width of the beam used It is followed by an immediate steep fall passing into a more gradual decline toward the surface (Figures 19 3 19-4) The ratio between the central and peripheral dose may be as high as 3 or 4 to 1 or even higher in esophageal carcinoma

Roughly speaking the ratio between the central maximal dose and the minimal surface dose—the degree of action —will be greater the immediate drop in intensity steeper, and the integral dose smaller when the penetration of the radiation is stronger the field is narrow the irradiated body small and its specific gravity low

Under the given circumstances the breadth of the field is of most significance Unlike cross firing on stationary fields this does not demarcate the irradiated from the unirradiated tissue it only influences the form of the dose distribution but in a decisive way With an increasing distance from the surface the individual points will remain longer in the beam Instead of a fall in the dose from the surface toward the depth a rise is obtained and this rise is more pronounced and steeper

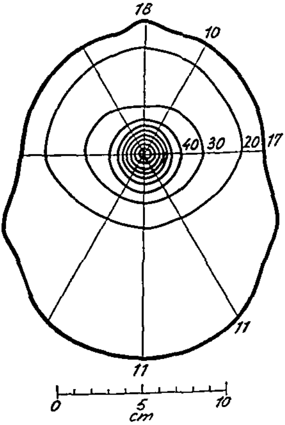


Fig 19-4 Dose distribution in the form of isodoses in the skull obtained by rotation irradiation of a pituitary tumor (axis field 10 × 40 mm) (Courtesy H Nielsen)

with narrow fields In other words in rotation therapy *ceteris paribus* narrow fields will contribute highly toward high tumor doses and at the same time spare the healthy surrounding tissue It thus follows that in rotation therapy the narrowest possible field should be used To be sure of hitting the target with the narrow beam fluoroscopic control is of great value

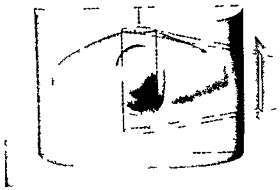


Fig 19.5 Three-dimensional dose distribution in a cylindrical phantom (with a diameter of 30 cm) Rotation irradiation with axis field 5 × 15 cm (dotted line) The shells represent dose levels of 100 per cent 80 per cent and 50 per cent (Courtesy H Nielsen)

Inasmuch as the dose distribution in rotation irradiation is favorably influenced by the penetrating power of the rays this special interest shall be maintained to clinical experiments on rotation therapy by supervoltage conducted by Trump and Hare Even roentgen rays at still higher voltage (10 to 30 million kv) might prove advantageous in rotation therapy (Laughlin and associates) It is therefore to be hoped that the betatrons and other apparatus for production of ray energy at this ultravolt level may be constructed and tested for this purpose Under such circumstances *fluoroscopic control is impracticable* and special efforts must therefore be made to obtain the exact distribution of the rotation axis

Concerning the height of the axis field the choice is made in the same way as in irradiation of stationary fields i e the height is chosen so that the entire tumor is covered by the field Owing to the decline in the dose delivered to the upper and lower limits of the field because of the divergence of the rays and the reduction of secondary rays in the periphery the field must be extra high projecting cranially and caudally at least 2 to 3 cm beyond the extent of the tumor This is permissible *especially as the height of the field* has no influence on the horizontal dose distribution In rotation irradiation of esophageal carcinoma high fields are moreover required to avoid pole recurrences because these tumors show a marked tendency to propagate through the lymphatics in a longitudinal direction Figures 19 5 and 19 6 based on experimental dose measurements give an idea of the three dimensional dose distribution in rotation irradiation with fields of different breadth They also illustrate impressively the diminution of the dose at the upper and lower limits of the axis field which should always be kept in mind

Eccentric localization of the tumor and consequently of the rotation axis will give essentially the same dose distribution curves as formerly described for centric rotation There will be a more or less pronounced displacement of the point of maximum intensity away from the axis of rotation toward the *nearest surface and the fall in dose will be*

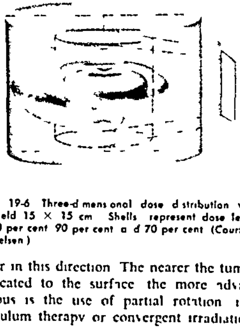


Fig 19-6 Three-dimensional dose distribution with axis field 15 × 15 cm Shells represent dose levels of 100 per cent 90 per cent and 70 per cent (Courtesy H Nielsen)

flatter in this direction The nearer the tumor is located to the surface the more advantageous is the use of partial rotation i e pendulum therapy or convergent irradiation

FLUOROSCOPIC VISUALIZATION OF THE TUMOR

The necessary condition for the continuous fluoroscopic control is that the tumor be

radioscopically visible or can be fluoroscopically visualized by some technical device For esophageal fluoroscopy the patient may swallow a small amount of thick barium This may be practiced not only in esophageal carcinoma but in several other inaccessible cancers As an example bronchogenic carcinoma If such a tumor cannot be directly visualized it may be marked by metallic clips inserted in the course of an exploratory thoracotomy or through the bronchoscope A tumor of the nasopharynx may be localized by a lead tipped sound introduced through the nose The same technic may be used to mark a tumor of the pituitary if the sella turcica or the air content of the sphenoidal sinuses is not directly visible as a landmark In this way also basal intracranial tumors may be marked Even tumors situated in voluminous parts of the body such as the rectum and the uterine cervix may be marked for fluoroscopic control by the introduction of metallic sounds or bodies

DOSE MEASUREMENTS AND CALCULATIONS

Calculation of the dose distribution is complicated and uncertain [19 23 24] This applies to homogeneous phantoms and even more so in vivo where the inhomogeneous consistence of the body with varying densities (lungs and bones) and irregular outlines tend to distort the intensity distribution curves (but as can be shown on suitable anatomic preparations not to a degree to make them illusory) It is therefore advisable whenever possible to try to obtain a control by direct measurement of the tumor dose with small ionization chambers introduced into the cavities in tubes or the like Neumann and Wachsmann have worked out a method for calculating the tumor dose from the exit beam dose The conversion of the exit beam dose is done by means of standard tables This method which allows for the differences of absorption in the irradiated tissues appears to be the most dependable one giving sufficiently exact data for the practical conduct of rotation therapy Yet it is advisable to supplement and control its results by direct measurement of the dose with condenser chambers inside the tumor area whenever possible

DOSAGE

By rotation irradiation it is usually possible to attain a tumor dose several times the skin dose As in supervolt therapy the latter has therefore lost its significance as a limiting and controlling factor and is of no practical interest in describing a treatment The tumor dose combined with the width of the axis field is of primary importance in defining the irradiation

The patients have shown unusual tolerance to rotation therapy which therefore may be administered with a considerably higher daily and total tumor dose than static field therapy Clinical experience must decide the size of the dosage adequate in tumors of different varieties and sites Care must be maintained to avoid a too rapid delivery, so that the reparative processes cannot keep pace with the destructive ones

DOSE FOR ESOPHAGEAL CANCER

In rotation therapy of esophageal carcinoma too intensive irradition (tumor dose 6 000 to 9 000 r or more in 20 to 30 days) though apparently tolerated by the patient may result in esophageal perforations and vascular ruptures [20 22 25] In our experience the most advantageous daily dose in attempts at curative rotation irradiation of esophageal carcinoma with axis fields of a width smaller than 5 cm is about 150 to 200 r and the total dose about 5 000 to 6 000 r administered in 5 to 7 weeks When using this dosage it has been found that the incidence of esophageal perforation and hemorrhage is lower even than occurs in cross fire irradiation At autopsy several of our patients dying from distant metastases have shown no remnant of the original tumor either macroscopically or microscopically The lumen of the esophagus at the former site of the tumor has been of normal width On close inspection a trace of cicatricial changes could be discerned in a small portion of the wall and on microscopic examination the tunica muscularis was found to have been replaced more or less by fibrous tissue These postmortem findings correspond to radiographic appearances in cured patients in whom deglutition is found to be practically normal

RADIATION DOSES FOR OTHER NEOPLASMS

Since clinical experience with rotation therapy in cancer other than that of the esophagus is less extensive any statement of dosage must be tentative Carcinomas of the lung rectum uterine cervix prostate and bladder appear to tolerate higher partial and total doses 200 to 300 r per day or a total dose of 6 000 to 9 000 r or more In rotation irradiation of very small tumors such as pituitary growths it seems possible to attain essentially higher tumor doses exceeding 10 000 r without cutaneous or systemic reactions Although this is of great theoretic interest the clinical experience is still too scanty to justify any determination of the most favorable partial and total dose in treating the various tumors of this organ This also applies to intracranial neoplasms

In purely palliative irradiation as for instance of patients in poor general health a total dose of 4 000 to 5 000 r is seldom exceeded

Concerning the width of the axis field it must be emphasized that it should always be as narrow as possible if only because of the decisive significance of this factor to the dose *distribution This is indicated also by clinical* observations In esophageal cancer the width of the axis field should not exceed 5 cm in some cases only 2 or 3 cm The author has successfully used even narrower fields thanks to the fluoroscopic control Tumors of more extensive lateral spread of course require broader fields As a general rule however it must be recommended to choose an axis field somewhat narrower than the transverse diameter of the tumor preferably not exceeding 5 or 6 cm although this gives a somewhat higher dose in the center than in the marginal zones of the tumor Apparently this is of no decisive significance and it may even be imagined to offer an advantage as the peripheral better vascularized and nourished tumor tissue may respond to smaller doses than the central part at the point of origin which usually exhibits infection and necrosis and which is in most cases the last part to yield to irradiation It seems important that by using a field not too wide it is possible to spare and preserve *the tumor bed a factor of the* utmost importance in healing

INDICATIONS FOR USE OF MOVING FIELD RADIOTHERAPY

Carcinoma of the intrathoracic part of the esophagus appears to be a particularly suitable object of rotational therapy because (1) this deep seated organ runs nearly in the long axis of the approximately cylindrical thorax and because neoplasms of the gullet display a tendency to spread in the longitudinal direction (2) the majority are squamous cell carcinomas of sufficient radiosensitivity and (3) the centering of the axis of rotation in the tumor can easily be controlled fluoroscopically simply by using the therapeutic radiation for this purpose In addition the clinical results of stationary field external irradiation and of attempts at intracavitary radium therapy have been unsatisfactory and until recently these tumors were inaccessible to surgery

As regards the delineation of the indications for rotational therapy versus surgical treatment the author shall confine himself to the personal statement that all cases of intrathoracic esophageal carcinoma considered inoperable should be given the chance of benefiting by rotation irradiation

Other Tumors For the time being while rotation therapy is in a stage of clinical experiment it would seem indicated only for inoperable tumors

As the rotation technic is designed to deliver a high dose to a small volume in a deep site it would *a priori* seem to be applicable chiefly in the treatment of tumors of the trunk In addition to bronchogenic carcinoma and other tumors of the thoracic cavity virtually all tumors occurring in the interior of the trunk may be submitted to rotation therapy cancer of the gastrointestinal tract—particularly the rectum—bladder prostate and true pelvis As far as cancer of the uterine cervix is concerned the results obtained by a combination of intracavitary radium therapy and external conventional stationary field irradiation are relatively good so that for the time being it seems reasonable to restrict the indication of rotation therapy to inoperable recurrences

But there may be reason to try rotation irradiation also in the treatment of tumors in parts other than the trunk such as the

cervical part of the esophagus hypopharynx larynx, mesopharynx nasopharynx and pituitary, all of which are rather easily visualized on the screen It is presumably also worth trying in the treatment of intracranial tumors and certain tumors of the extremities such as osteosarcoma of the femur

Thus the indications may theoretically be wide in fact corresponding to those of cross fire deep therapy on multiple fields, as rotation may in a way be considered a further elaboration of this technic The following general rules may be set up The smaller i e narrower the tumor the more central its localization in the part concerned the easier its fluoroscopic visualization or the easier and more accurate the placement of the rotation axis the more reason there is to consider rotation therapy

Clinical Observations

The account of the clinical observations during the performance of rotation therapy is based mainly on personal experience from more than 600 cases of esophageal carcinoma thus treated

LOCAL AND GENERAL REACTIONS

What strikes one particularly is the tolerance exhibited by the patients both as regards the general condition and the local reactions in the skin and other irradiated tissues It may be said that this technic affords a means of delivering a sufficiently high and localized tumor dose to the esophagus and its immediate surroundings without too severe impairment of the patient s general and local condition

The skin reactions are moderate corresponding to the favorable even low dose received They appear usually in the form of slight or moderate dry epidermitis Later the skin of the radiated zone often resumes its normal appearance

Reactions in deeper irradiated structures are also mild Radiation pneumonitis and lung fibrosis are virtually unknown owing to the even low dose distribution outside the axis field Also cardiac symptoms and electrocardiographic changes do not occur Fairly often the treatment may be accompanied by a fall in blood pressure which however seldom gives rise to subjective complaints Radiation myelopathy and radiation osteitis of the spine have not been observed

The response of the tumor is soon apparent and may be followed during the daily screening control In two thirds of the total cases and in four fifths of those in which a curative treatment was attempted complete or nearly complete primary freedom from symptoms was obtained i e normal or almost normal deglutition and roentgenographic signs of marked improvement of the passage often with a normal mucosal pattern Gastrostomy even preliminary, was rarely required

Complications from too rapid a breakdown of the tumor tissue such as hemorrhages and perforations may be kept at a low level by avoiding too high daily and total doses as mentioned above

Observations during rotation therapy of tumors in other sites are scant scattered and selected On the whole however they serve to confirm the finding of high tolerance slight local and systemic reactions and marked response

RESULTS

As will be seen from Table 19 1 the clinical results of rotation therapy in inoperable intrathoracic esophageal carcinoma are still mostly palliative the improvement obtained being in most cases temporary Recurrence in the esophagus is not uncommon, most of them developed above or below the primary stenosis and sometimes yielded to another course of palliative rotation therapy Many patients were able to swallow to the very end and death was in most cases due to metastases and cachexia

In the 6 patients living more than 5 years the histologic diagnosis was squamous cell carcinoma Adenocarcinoma of the esophagus and cardia or carcinoma of the gastric fundus did not in any case benefit by rotation therapy longer than 15 months

A rather marked drop in the survival will be noted in the third year which is due to metastases and local recurrences that may appear even at the end of 3 and 4 years Thus the 5 year salvage of the total number is below 3 per cent

Despite a higher primary mortality (owing to perforations and other complications) in

TABLE 19 1 —ROTATION TREATMENT OF 242 PATIENTS WITH CARCINOMA OF THE INTRATHORACIC ESOPHAGUS RADIUM CENTER COPENHAGEN
(From 1941 to 1944)

		Total patients 242	*No of patients treated 231*	*No of patients on whom attempt at cure was made 185*	*No of patients who were fully treated 126*
Alive years	*Number*	*Per cent*	*Per cent*	*Per cent*	*Per cent*
1	59	24	25	31	47
2	30	12	13	16	24
3	14	6	6	7	11
4	9	3.5	4	5	7
5	6	2.3	2.6	3.2	4.8

All cases were considered inoperable no case was refused irradiation
All cases alive more than 5 years were microscopically verified (squamous-cell carcinoma)
One fourth of all patients and half of the fully treated patients were alive 1 year
One eighth of all patients and one fourth of the fully treated patients were alive 2 years
Six per cent of all patients and 11 per cent of the fully treated patients were alive 3 years
2.3 per cent of all patients and 4.8 per cent of the fully treated patients were alive 5 years

carcinomas located in the upper and middle thirds than in the lower third of the intrathoracic esophagus the 2 and 3 year survival rates seems to be nearly the same for all three localizations (when adenocarcinoma of the lower third is excluded Table 19 2)

The problem of regional lymph node metastases would seem to present most difficulty in rotation therapy of esophageal carcinoma as it calls for broader axis field thereby counteracting the advantages of the dose distribution in rotation irradiation

The results of rotation therapy of other tumors are still few and scattered No statistics can be presented The author has treated a limited number of selected cases of inoperable bronchogenic carcinoma (mainly after artificial pneumothorax) So far only palliative results have been obtained As might be expected the same applies to carcinoma of the rectum and adenocarcinoma of other sites

PENDULUM OR ARC IRRADIATION

Description

In this form of moving field irradiation originally advocated by Kohler and associates the tube moves while the patient is in the motionless horizontal position The movement of the tube is usually restricted to a part of a circle (pendular movement) about a horizontal axis that may be set at varying levels over the table The central ray may be at a right angle on the axis of rotation or it may

TABLE 19 2 —ROTATION TREATMENT RADIUM CENTER COPENHAGEN SURVIVAL RATES ANALYZED ACCORDING TO DIFFERENT SITES OF INTRATHORACIC ESOPHAGEAL CARCINOMA

Location	*Number of patients*	*Per cent of all cases*	*Alive 5 years or longer*
Jugular vein to bifurcation of trachea	26	10	1
At the bifurcation of trachea	94	40	2
Bifurcation to cardia	71	30	2
At the cardia	51	20	1

be more or less oblique The center of the tumor is in the axis of the pendulum This adjustment, effected by movements of the apparatus and the table must be extremely accurate and therefore often requires radiographic or fluoroscopic control Continuous fluoroscopic control, however, is not practicable *during the irradiation and it is not* absolutely necessary considering that the patient

Fig 19 7 Siemens equipment for pendulum irradiation (After Kohler)

is motionless It is a *sine qua non* that the axis of the pendulum is accurately centered and that this may be reproduced without too much difficulty at each sitting Successive arc irradiations may be performed at different angles on the horizontal axis through the tumor

Apparatus

Various types of available units may be equipped for pendulum irradiation with fairly simple means Ready made sets are marketed (Figures 19 7 and 19 8) which are provided with a visual localizer for centering on the surface One is fitted with a mechanical contrivance by which the horizontal arm carrying the tube hood is movable in different directions This movement may be free or coupled so that the central ray can be directed all the time at the same point The unit contains a special table with hydraulic level adjustment

Principles and Practice

The dose distribution in pendulum irradiation and its dependence on different factors is similar to that in rotation or convergent irradiation For details the reader is referred to the papers by Kohler *et al*

The choice of the area of the axis field and the dosage are dependent on the same principles as in rotation therapy

Dose measurements on phantoms form the basis of dose calculations in practice As in rotation therapy they must, as far as possible be controlled by measurements of the tumor dose in each individual case

Indications

The indications are the same as stated under rotation therapy This technic is especially suitable in dealing with *tumors in* eccentric situations close to the surface (such as lymph node metastases) Pendular irradiation of these sites does not achieve merely a marked sparing of the structures superficial to the tumor but deep to the tumor there is a steep fall in the dosage owing to the divergence and absorption of the radiation

Provided the axis of the pendulum is aligned with sufficient accuracy, arc irradiation is no doubt the method of choice in certain special cases *In measurements on phantoms* the author found that pendulum irradiation of 180° (or slightly more) about each of two symmetrical axes equidistant (2 to 4 cm) from the median plane would give a favorable dose distribution in the true pelvis The three dimensional intensity distribution assumes the shape of a saddle In the frontal plane the dose distribution shows a rather low level around the mid line, increasing considerably toward the lateral pelvic wall and falling peripheral to the latter In the sagittal plane the maximum value occurs about the mid line showing a rather steep fall anteriorly toward the bladder and posteriorly toward the rectum Such a dose distribu

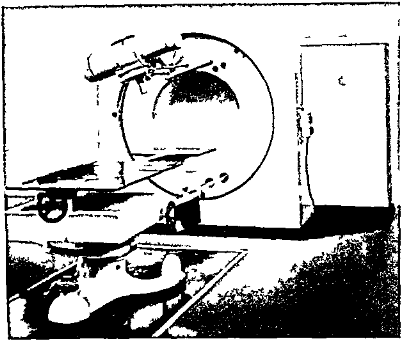


Fig 19 8 Muller equipment for moving field irradiation

tion would seem ideal in the combined roentgen and radium therapy of cervical carcinoma

Clinical Results

Clinical results cannot yet be reported as the numbers treated are too small

CONVERGENT IRRADIATION

Description

In convergent irradiation the patient is also in the motionless horizontal position (sitting in exceptional cases) The tube moves about an axis forming an angle on the long axis of the body The central ray is oblique on the rotation axis

Apparatus

Green and collaborators rotate the horizontal patient about a vertical axis

In the Siemens convergent irradiation unit which presents an elegant technical solution of the problem the tube moves over a spherical segment in the way that the small round field

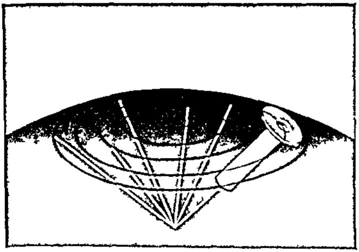


Fig 19 9 In the Siemens unit for convergent irradiation the field of entry moves in a spiral on the surface while the central ray is directed all the time at the same point in the depth the center of the convergent and rotating beam (Courtesy F Wachsmann)

of entry describes a spiral on the skin During this movement the central ray is directed against the same point of convergence in the depth (Figure 19 9) The entire circular irradiated field receives approximately the same dose The center of convergence may be placed at varying depths below the surface by distance tubes of varying length By means of various circular diaphragms moving with the tube tumor fields of a diameter from 2 to 10 cm may be obtained

Dose Distribution

Figure 19 10 conveys the type of the dose distribution obtainable with the Siemens convergent irradiation unit The smaller the diaphragm the greater the relative depth dose (up to 400 per cent) An even higher depth dose may be obtained by setting up another field of convergence on the opposite side of the body

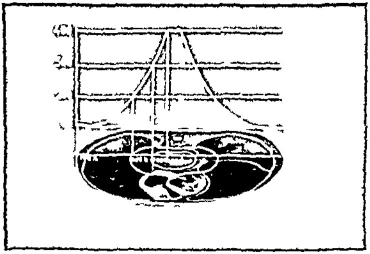


Fig 19 10 Type of dose distribution (isodoses) obtained with the Siemens convergent irradiation unit (Courtesy F Wachsmann)

Dose Measurement

In practice, the dose distribution is measured on the basis of standard isodose charts resulting from measurements on phantoms and calculations Corrections must be made for the volume and consistency (bones lung tissue) of the part concerned

Conduct of Treatment

After a suitable diaphragm and distance tube have been selected the ray is centered on the tumor as accurately as possible by means of centering and marking devices that serve also to reproduce the setup (Figure 19 11) The dose is varied by altering the tube current, as the time of revolution is constant

EVALUATION OF THE DIFFERENT FORMS OF MOVING FIELD IRRADIATION

It is still too early to compare the three forms of moving field therapy All three aim at the same goal of increasing and concentrating the depth dose within the tumor area and of leveling off the dose outside this area

This end may be attained by various more or less elaborate and intricate means but in any case the accurate placement of the axis of motion is of capital significance Failing this the entire procedure becomes illusory while imparting a false feeling of security

For the moment it would appear most advantageous to choose the simplest method, affording the safest control of centering i e rotation with constant fluoroscopic control

Theoretically the other forms of moving field therapy are excellent and may furnish a multitude of favorable dose distributions applicable in practice Their advantage is that they may be used for all sites not only the minority of cases in which the tumor may be visualized Moreover the motionless horizontal position of the patient guards against displacement during the irradiation

It may seem questionable however whether

the technical equipment available today affords a quite sufficient guarantee of accurate alignment of the axis in practice and whether it permits an accurate reproduction at each sitting The precision devices required for this purpose concerning the suspension of the tube as well as the movements of the table call for further elaboration and testing Like

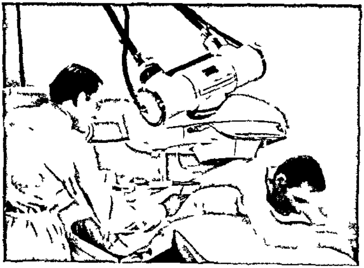


Fig 19 11 Alignment of the center of convergence on the patient by means of a centering device (Courtesy Siemens)

wise the possibilities of radiographic and fluoroscopic control of the centering must be improved and solved technically for practical purposes These are relatively simple mechanical and technical problems that can be and probably will be solved now that the manufacturers are taking an interest in the production of equipment for moving field therapy

A more difficult physical problem is presented by the practical determination of the integral dose a highly desirable factor in deciding which form of moving field therapy is to be applied in each individual case

It is clear that mechanical and technical improvements alone cannot bring the final solution of radiotherapeutic problems But as long as practical radiotherapy of cancer consists in delivering a certain dose of radiation to a certain volume of tissue the time and care expended on attaining the most favorable solution of this limited problem can hardly be repented Only by doing so can we hope to be able to relate the therapeutic results to the dose and dose distribution and to create the necessary basis for utilizing experimental radiobiologic experiences in clinical practice

It must be admitted that the radiotherapeutic technic is still in a relatively primitive stage even the beam direction technic on multiple stationary fields In comparison with the latter moving field irradiation affords evident physical advantages The question remains whether it may be elaborated in practice to afford sufficient precision and in a technical form that does not require more time and energy

CHAPTER 20

The Clinical Application of the Betatron in the Treatment of Cancer

Roger A Harvey
and
John S Laughlin

DESCRIPTION OF THE BETATRON

The betatron was so named by its inventor Professor D W Kerst (1941) because it is an electron accelerator A horizontal cross section of its accelerating tube the donut is shown in Figure 20 1 Electrons are injected

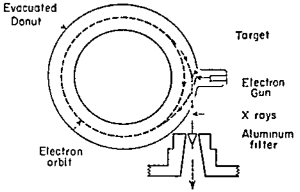


Fig 20 1 Diagram of the acceleration of electrons in a betatron and the production and collimation of the x ray beam

intermittently into the tube from the electron gun These bursts of electrons are continuously accelerated in a circular orbit by the action of a changing magnetic field After the electrons have been accelerated to a high energy approximately 24 mev in our medical betatron they are deflected and strike the target The sudden stopping of these high energy electrons in the target produces x rays with maximum intensity in the forward direction These x rays have a continuous energy spectrum extending from a maximum of about 24 mev to the lowest energy transmitted through the porcelain wall of the donut As shown in Figure 20 1, the x rays pass through a differential aluminum filter and also through a lead collimator The collimator defines the beam and is easily and quickly changed to obtain different field sizes Our smallest field is 1 cm in diameter and the largest 15 cm at 80 cm from the target Intermediate field sizes are available and both circular and rectangular fields are used in clinical application The differential filter is constructed so as to make the intensity of the beam uniform across the field This produces flat isodose surfaces in the patient

PHYSICAL ADVANTAGES IN BETATRON X RAY THERAPY

The betatron x ray beam has several distinct advantages for application to therapy

Depth Dose Distribution

The depth dose distribution produced in the absorption of these high energy x rays reaches a maximum about 4 cm below the surface of the body and has minima on both the entrance and exit surfaces A typical distribution is shown in curve *A* of Figure 20 2 for a 5 cm diameter field at 80 cm target skin distance Precise dosage measurements [9, 10] have established that though there is dependence of depth dose on field size it is limited and small in comparison with the strong dependence typical of lower energy x rays A significant feature of curve *A* in Figure 20 2 is the high percentage dose at considerable depth due to the penetration of the high energy x rays For comparison curve *B* [17] in Figure 20 2 is the depth dose dis

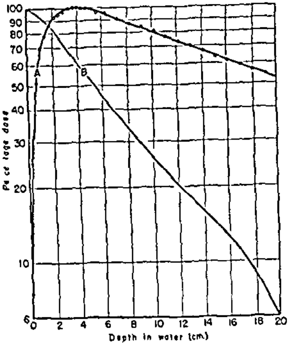


Fig 20 2 A Depth dose distribution produced in a water phantom by 24 mev betatron x ray beam 5 cm in d ameter at 80 cm T S D B Curve plotted from depth dose data obtained with a 200 kv x ray beam 1 mm Cu filter 1 mm Cu H V L 5 cm d ameter at 80 cm T S D (From E H Quimby [17] page 402)

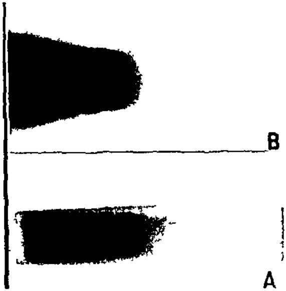


Fig 20 3 A Film exposed in phantom to x ray beam from 24 mev betatron 5 cm field diameter 80 cm T S D B Film exposed in same phantom to x ray beam from 200 kv x rays 1 00 mm Al and 0 5 mm Cu filter 5 cm field diameter 80 cm T S D Black l ne along left side shows edge of film or skin surface (From Harvey Haas and Laughlin [4] courtesy Rad ology)

tribution for a 200 kv x ray beam 5 cm in diameter at 80 cm target skin distance

Side Scatter

At these energies side scatter is greatly minimized which permits a greater degree of localization of the beam inside the body This feature as well as the penetration is displayed qualitatively in Figure 20 3 The lower film (*A*) was exposed in a phantom of bodylike material to the betatron x ray beam The maximum intensity below the surface the minimal surface intensities great penetration and sharp definition are apparent The upper film (*B*) was exposed to a 200 kv x ray beam with

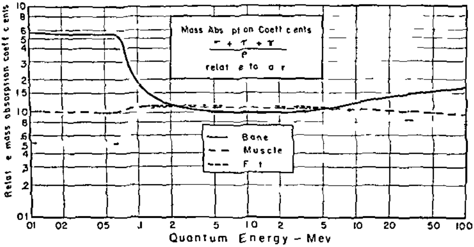


Fig 20-4 Mass absorption coefficients for i dicated quantum energies in bone fat and muscle relative to a r Absolute *absorpt on in ergs/gram* roentgen in these media can be obta ned by mult plying the values in the graph by 83 7 ergs/g am roentgen (From Laughlin [11] courtesy *Nucleonics*) For results of a similar *calculation see* H E Johns *Medical Physics* Chicago Year Book Publishers Inc 1950 vol 2 p 791

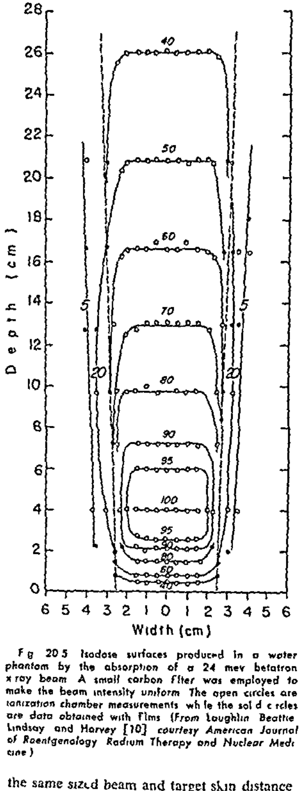


Fig 20 5 Isodose surfaces produced in a water phantom by the absorption of a 24 mev betatron x ray beam A small carbon filter was employed to make the beam intensity uniform The open circles are ionization chamber measurements while the solid circles are data obtained with films (From Loughlin Beattie Lindsay and Harvey [10] courtesy American Journal of Roentgenology Radium Therapy and Nuclear Medicine)

the same sized beam and target skin distance with 0 5 mm Cu and 1 0 mm Al filtration The differences in distribution of energy are obvious

Absorption in Body Tissues

At the betatron energies the concentration of ionization in bone per gram roentgen is not significantly greater than that in muscle and fat The basis for this is illustrated in Figure 20-4, in which the mass absorption coefficients in bone, fat and muscle relative to air have been plotted as a function of energy The curves are an extension to higher energies of absorption curves by Spiers The construction of the curves required calculations of the contribution by both the scattering effect and pair and triplet electron formation effect The integration of these relative mass absorption coefficients over the betatron effective x ray intensity spectrum yield the effective relative mass absorption coefficient in bone, muscle and fat Values of these are tabulated in Table 20 1 For comparison values calculated in a similar manner for 200 kv x ray generator and 50 mev betatron machines are also presented

Isodose Surfaces

Since the output from betatrons is relatively high it is convenient to use differential filters to produce beams with uniform intensity over the field The filter material is of low atomic number either carbon or aluminum in order to absorb low energy x rays more than higher energy x rays and in order to minimize th number of neutrons to which the patient is exposed A typical isodose distribution for a single field is shown in Figure 20-5

CLINICAL APPLICATION OF BETATRON THERAPY

Historic Introduction

The first patient was treated with a 20 mev betatron in the Department of Physics at the University of Illinois in 1948 [16] In the spring of 1949 the Physics Department at the University of Saskatchewan in conjunction with the Saskatchewan Cancer Commission inaugurated part time patient treatment with a similar betatron [5] Our local experience started in the summer of 1949 when the University of Illinois College of Medicine installed the first betatron in a therapy department and restricted its use to medical treatments and closely related research problems Since then we have treated 40 patients All patients have received treatment with the x ray beam, but the electron beam has been utilized to evaluate

TABLE 20 1 —EFFECTIVE MASS ABSORPTION COEFFICIENTS PER GRAM ROENTGEN RELATIVE TO AIR FOR CONTINUOUS X RAY SPECTRA

	Maximum energy of x ray spectra		
Absorbing material	*200 kv (1 mm Cu filter)*	*23 mev (5 cm Al filter)*	*50 mev (unfiltered)*
Bone	2 07	1 14	1 44
Muscle or tissue	1 10	1 09	1 06
Fat	95	1 06	1 02

This table displays the effective relative absorption coefficients in bone mu cle and fat for the x rays generated by accelerators of the indicated maximum energies
SOURCE From Laughlin [11] (*Courtesy Nucleonics*)

problems of application and to make preliminary observations on the biologic effects of this second type of beam for clinical evaluation Figure 20 6 illustrates the physical plant of our betatron installation

Selection of Patients

There is no evidence to date of altered sensitivity of different types of neoplasms to the betatron beam The total size of the neoplasm must be less than the largest field size which is 15 cm at 80 cm target skin distance Metastatic or disseminated types of neoplasms have not received greater relief from this type of treatment to warrant additional effort for this treatment to date The final factor is a deep location of the tumor

Preparation of Patients

Particular stress is placed upon localization of the tumor and the size and shape of the body at the cross sectional levels of the tumor The degree of penetration increases the number of fields that can be used but the somewhat limited field sizes and the lack of significant side scatter make it dangerously easy to miss the tumor from remote entrance fields These distant fields may be undesirable from the standpoint of volume dose to intervening normal tissues or high dosage to a specific vital structure in its path such as the esophagus and spinal cord in chest cases Otherwise the plan of application is similar to that for more conventional radiation therapy

Figure 20 7 shows treatment planning for

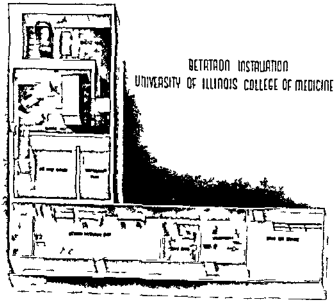
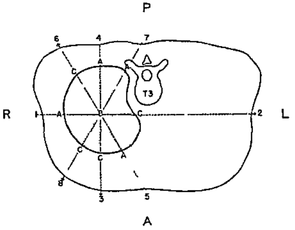


Fig 20 6



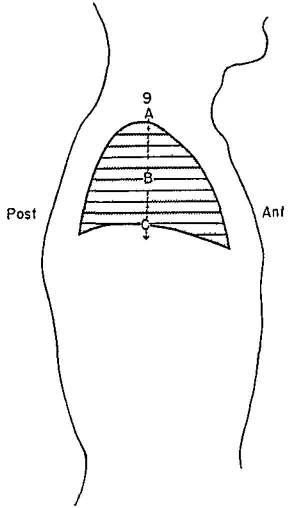


Fig 20 7 (*Left right*) Treatment planning for an upper lung neoplasm is shown with numbered sites representing entrance and exit beam zones Depths A B and C indicate zones to which delivered doses should be similar Entrance sites 2 and 1 would be used least of all because of large volume dose to normal tissues in the path of the beam (*From* Harvey Hass and Laughlin [4] *cou tesy Radiology*)

an apical lung tumor The largest amount of treatment would be given from points 3 4 5 6 7 and 8 The other points of entry are used to a lesser extent (particularly 2 and 1) for it is doubtful that the net gain of irradia tion in the tumor warrants the risk of such a high absorption in the normal tissues We rarely use less than 5 or more than 9 entrance fields for each tumor [4] The construction of a typical isodose chart for a bronchogenic cancer is shown in Figure 20 8

Reactions in the Patient

The lack of reactions or the minimal extent of these is striking with the betatron There are no sensations during or immediately after treatment Epilation in the treated areas is more pronounced than erythema but hair has regrown nicely in epilated zones The erythema has been mild and dry even in the most heavily irradiated areas [2] Only 2 pa tients have complained of nausea Dysphagia has been troublesome when the esophagus was in the path of several converging beams *Intracranial pressure has diminished* during treatment of five brain tumor cases and in creased in one Delayed reactions have not

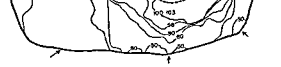


Fig 20 8 Isodose contours in a plane passing through tumor

appeared in the year and a half of our treatment experience

Results of Treatment

The relatively small number of patients treated the variety of neoplasms tested and the extent of the neoplastic disease at the time treatment was started do not permit conclusive opinions at this time A few observations are heartening

Oral neoplasms have shown extensive sloughing of the diseased tissues when about one third of the total dose has been delivered but hemorrhage has not occurred [3] Subsequent healing has been good and can be attributed to the sparing effect of the dose distribution on adjacent normal tissues

Patients with intracranial neoplasms have tolerated treatment very well Their post treatment course has been generally one of improvement in most re pects but late results are not expected to be outstanding The original size of most of these neoplasms was such that considerable functioning tissue was either destroyed or irreparably distorted prior to treatment

The bright spot in response of chest neoplasms has been chiefly in the apical area where bone destruction and pain are prominent Figure 20 9 shows one such patient before and on the last day of treatment The original degree of supraclavicular swelling and venous stasis are in sharp contrast to the findings at the end of treatment Erythema and pigmentation are moderate and pain constant before treatment began to ease away during treatment and was widely intermittent at the end of treatment Another similar patient treated earlier by the same method has shown recalcification of the eroded rib Figure 20 10 and complete relief of pain 6 weeks after treatment Recalcification was first observed 4 months after treatment and has increased steadily The soft tissue apical density continues to lessen in size Experience with bronchogenic carcinomas located in central and lower lung areas has not been encouraging so far but the cases we have seen have been inoperable and extensive Limited experience with lymphoblastomas and oat cell carcinomas has shown expected regression of the treated tumors but the natural history of these tumors makes it difficult to keep up with their reappearance elsewhere in the body

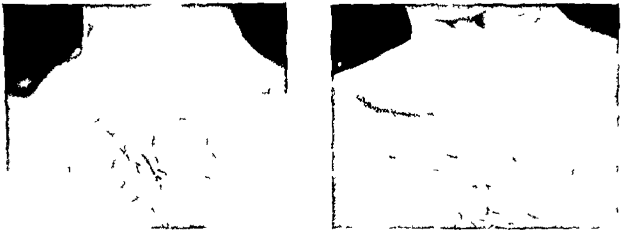


Fig 20 9 The pretreatment photograph (left) shows the degree of soft tissue swelling and venous distentions with a Pancoast tumor The other photograph (right) shows same area on the last day of treatment A slight degree of pigmentation and local ep lation is present In 20 treatments over a period of 28 days 11 063 betatron r were delivered to the tumor Eight fields were used

Treatment of abdominal tumors has been limited to terminal bladder cancer one cervix cancer one inoperable adenocarcinoma of the head of the pancreas and a metastatic oat cell carcinoma to the upper abdomen Some of these patients have had mild radiation nausea or diarrhea but these symptoms were markedly diminished by reducing the total daily dose and promptly disappeared at the end of treatment Hematuria ceased during treatment of the bladder cancers and one autopsy showed marked and highly selective

Fig 20 10 Another Pancoast tumor patient with typ cal apical density and rib destruction before treatment is shown in the upper roentgenogram Decreasing soft tissue density and recalcificat on of the rib (*lower*) are shown 8 months after treat ment with 9 081 betatron r to the tumor in 23 treatments over a period of 32 days S x felds were used (*From* Harvey Haas and Laughlin [4] *courtesy Radiology*)

destruction of the anaplastic cancer as com pared with adjacent normal tissues which appeared to be relatively unaffected [4] The cervix case showed good distribution of the internal reaction regression of the local tumor but some lateral induration since which may be due to inadequate treatment in the early stages of our experience The pancreas tumor patient tolerated treatment without a com plaint or symptom has been comfortable and has worked regularly for more than 6 months since treatment A metastatic oat cell tumor within the abdomen regressed nicely under treatment but there are other evidences of the disease in the same patient

We have not had experience with tumors of the extremities or bones either primary or metastatic but hope to test cases of this type

Any differences that we have observed thus far between conventional x ray therapy

Group 5

Treated: October 1950

Patient	Age	Location	Type	Total tumor dose r	Fields	Treatments	Overall time days	Comments
H.B	57	Lung	Pancoast	11 063	8	20	28	Living; Swelling and pain disappeared Tumor shrinking Working gaining weight
A D	60	Lung Nodes Nodes	Lymphosarcoma	10 010 2 600 4 350	7 1 1	21 3 6	32	Living No visible or palpable residual Abdominal metastasis
J P	69	Lung	Bronchogenic	10 240	7	21	32	Living Weakness and dysphagia
A.B	64	Brain Temporo-parietal	Astrocytoma	7,990	8	16	21	Living No increase in pressure Satisfactory
J T	57	Lung	Oat cell	9 505	6	25	35	Living Lungs neck nodes and mediastinum clear Liver metastases now
V S	65	Tongue	Epidermoid	10 037	6	18	24	Living Regressing rapidly
T P	21	Brain	Glioblastoma	795	2	2	2	Treatment discontinued extreme agitation
E W	56	Brain	Glioblastoma	7 560	9	15	21	Living Prolapse increasing
L G	64	Lung	Bronchogenic	1 315	3	3	7	Failed rapidly Died outside hospital

Fig 20 11 A brief summary of the details of treatment of one group of patients (*From Harvey Haas and Laughlin [4] courtesy Radiology*)

and betatron x ray therapy can be largely explained on the basis of delivering an accurate dose to the tumor while sparing normal tissues to a significant degree This advantage is best appreciated by reviewing Figures 20 11 and 20 12 and 20 13 The first figure gives general data on a group of patients treated in October 1950 Figure 20 12 shows the dose variation in skin tumor, and average dose in healthy tissue that was unavoidably irradiated Only the fifth patient in this group experienced radiation sickness and it will be noted that his healthy tissue dose was much larger than that of any of the other patients Figure 20 13 shows the integral dose for tumor and healthy tissue irradiated

	Skin Dose (roentgens)		Tumor Dose (roentgens)			Average Dose in Irradiated Healthy Tissue (roentgens)
Patient	Highest	Lowest	Highest	Lowest	Center	
H B	2,020 18 3%	620 5 6%	11 073 100%	10,420 94 4%	11 073 100%	856 7 7%
A D	1 595 16 1%	584 5 9%	10 100 102%	9,780 98 7%	9 914 100%	1513 15 3%
J P	1 990 19 4%	707 6 9%	10 450 102%	9 120 89%	10 40 100%	1567 15 3%
A B	1 545 19 1%	396 4 9%	8 170 101%	7 970 98 5%	8 090 100%	1028 12 7%
J T	2,360 24 7%	1 338 14%	9 870 103 %	9 370 98 2%	9 5 5 100%	2836 29 7%
V S	1 940 19 3%	93 5 9%	10 03 100%	9 620 95 8%	10 035 100%	662 6 6%
E W	1 170 15 2%	762 9 9%	7 840 101 %	7 720 100%	7 720 100%	683 8 9%
% Relative to Center of Tumor Dose						

Fig 20 12 Shows dose variation in different tissue zones of 7 patients from Figure 20 11 Skin dose variations are due to difference between entrance and exit dose levels and to what extent entrance and exit fields were superimposed in treatment The small *variation in dose* at different levels of the tumor and the low dose *in healthy tissue in the path of the beam are particularly* significant The fifth patient in this group had several areas of the body treated and *this accounts* for the rather high healthy tissue dose (*From Harvey Haas and Laughlin [4] courtesy Radiology*)

Integral Dose (megagram roentgens)

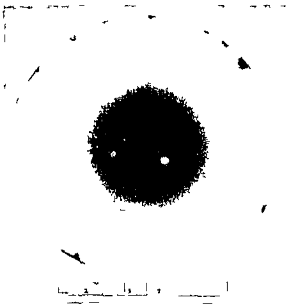
Patient	Total Volume	Tumor Volume	Irradiated Healthy Tissue Volume	Average Dose in Irradiated Healthy Tissue (roentgens)
H B	15 219	6 925	8 294	6 6
A D	1 00	4 973	16 527	1 513
J P	51 168	23 785	27 383	1 567
A B	1 240	4 470	7 770	1 0 8
J T	4 825	19 690	5 1 5	2 855
V S	10 356	5 075	5 261	662
E W	11 050	5 940	5 110	683

Fig 20 13 Shows the integral dose in terms of megagram roentgens as related to volumes of different tissue *in the beam path* (*From Harvey Haas and Laughlin [4] courtesy Radiology*)

CURRENT DEVELOPMENTS

Rotational Therapy

In certain cases rotation of the patient is practicable as presented by Trump and Hare and by us at the Sixth International Congress of Radiology in London in 1950 Rotation simplifies the attainment of a multiple field treatment Although rotational methods with the betatron would not improve the dose distribution greatly over that obtained with multiple field technic the greater convenience appears attractive Figure 20 14 shows the dose distribution by film density and experimental graph obtained from a cylindrical body rotated in the path of the betatron x ray beam [8] Similar localization results from our present multiple field technic but with greater daily effort A full sized phantom man is being used to explore rotational technics to a greater degree



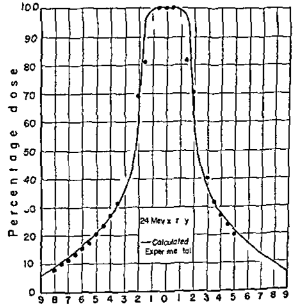


Fig 20 14 (*Left*) Film exposed in cylinder rotating in path of 3 cm diameter betatron x ray beam (*Right*) The solid points are density measurements of film at left The solid curve is a theoretical calculation (*From* Laughlin Harvey Haas Lindsay and Beattie [8] courtesy *American Journal of Roentgenology Radium Therapy and Nuclear Medicine*)

Electron Beam

The direct electron beam from the betatron is also of interest in therapy Electrons are absorbed differently from x rays with the result that the depth of penetration of an electron beam in tissue has a definite limit Consequently the exit dose is negligible A magnetic shunt method is employed to extract the beam [18 19] Figure 20 15 shows a film exposed parallel to the path of an electron beam of 18 1 mev energy and 9 cm diameter field It demonstrates the definite range of electrons in contrast to that of x rays in Figure 20 2 Depth dose data obtained from various energies are shown in Figure 20 16 The field size was 9 cm in all these and the size can be varied conveniently Tissue tolerance studies are well along now and an early human application of the electron beam will be made to breast cancer Such an application takes advantage of the unusual depth dose distribution of this beam

Several hundred patients have been treated with our betatron and the added number of patients with longer periods of observation have not changed our original observations as outlined in this chapter We have reduced the amount of daily dose and the eventual total dose as well as lengthened the over all treatment time in order to minimize late radiation effects in deep tissues that were close to tumor bearing regions and therefore unavoidably irradiated Our associate Dr Lewis L Haas has extended his application of the x ray beam in the form of spray irradiation to several patients with widely disseminated neoplasm

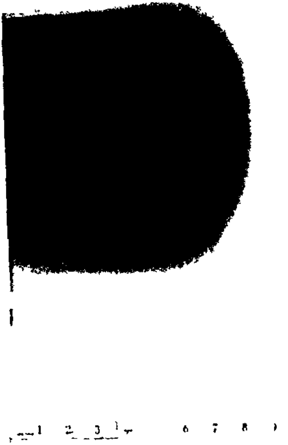


Fig 20-15 Film exposed parallel to electron beam of 18 1 mev energy incident on a pressedwood phantom (From Laughlin Harvey Haas Lindsay and Beattie [8] courtesy *American Journal of Roentgenology Radium Therapy and Nuclear Medicine*)

and has demonstrated some striking regressions although the effect is admittedly temporary and palliative He has also treated several patients with surface and subsurface cancers with the electron beam and conclusively demonstrated its power to destroy radiation sensitive neoplasms and its main advantages—to be sparing of vital normal structures beneath a treated zone with a limited surface area and depth volume of reaction—both of which minimize discomfort to the patient and enhance healing

Absolute Dose Measurement

In all cases treated with the betatron so far the absolute dose has been expressed in terms of an arbitrary roentgen This roentgen is defined as the reading of a 25 r Victoreen thimble chamber at the point of interest The output

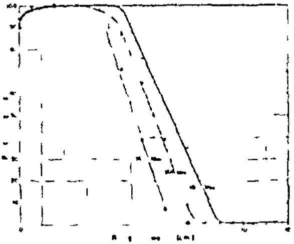


Fig 20-16 Depth dose measurements in a water phantom exposed to a 9 cm diameter electron beam of the indicated energies (From Laughlin Harvey Haas Lindsay and Beattie [8] courtesy *American Journal of Roentgenology Radium Therapy and Nuclear medicine*)

of the betatron is ordinarily measured with a 25 r chamber at 84 cm target distance and centered in an 8 cm cube of lucite The biologic effectiveness of this unit varies from about 0 7 to 0 5 of that of the roentgen measured at lower voltages [1 2 3 4] A more fundamental and physically significant unit of dose would be the actual ergs of energy dissipated per gram of substance at the point in question A calorimetric technic employing thermistors has been developed and is being used to accomplish the direct measurement of dose in terms of ergs per gram

Clinical Application of Radium

CHAPTER 21

Methods of Applying Radium in Cancer Therapy

J L Dobbie

INTRODUCTION

The methods of radium treatment of malignant tumors at present in use have been practiced for the last twenty or twenty five years Naturally a number of methods and applications have been discarded during that period More important have been two other factors the gradual agreement that gamma ray dosage can be measured in roentgens and the recognition that for an effective command of the resources of radium therapy a dosage system that can be understood and applied by the clinician himself is indispensable At the same time the condition treated has come to be almost exclusively squamous carcinoma The sites treated are limited by the accessibility of the tumor by its size and in practice by the existence in some cases of an equally good but simpler method of treatment The accessible sites are skin mouth uterus and breast and these with the important addition of the bladder which can be exposed surgically are the typical sites for the employment of radium

Thus radium therapy has arrived at a stability or even orthodoxy which permits of intelligible description and communication and which provides a background of possibilities in the mind of the clinician when the all important choice of treatment has to be made This chapter will be an attempt to review these possibilities in general terms and to define the indications for particular methods It is of course not intended as a complete guide For greater detail reference may be made to Ralston Paterson s *The Treatment of Malignant Disease by Radium and X rays* [10]

The methods of brachyradium that is to say needle implants intracavitary methods and superficial applicators (molds) will be presented Although radium is referred to throughout other sources of γ rays of the same intensity can easily be used instead Thus Co^{60} can replace radium in all its applications and small plated gold slugs (Au^{198}) with a half life of 2 7 days have been used to replace permanent implant of gold seeds containing radon[11]

Brachyradium methods bear the marks of their ancestry in using (usually) multiple small units of radium with a dose time relationship founded on the results of early empiricism Because of this and also from necessities inherent in their mere mechanics they are subject to certain common limitations and have some common characteristics

1 Accessible tumors only can be treated but this usually means that the tumor can be the more exactly defined

2 Effective dosage is restricted to a plane of little depth or to the immediate proximity of implanted needles but because of this restriction the dose allowable is a high one

3 The dose rate is planned to result in the administration of the whole dose in 6 to 10 days

Some of the implications of these characteristics therefore are extremely favorable in particular the combination of a high dose strictly confined and accurately placed represents the ideal of radiotherapy for squamous carcinoma as at present conceived

The Statement of Dosage

An early generalization on the importance of time should be made here

In x ray therapy and in gamma ray therapy it is the invariable practice to relate the dose given with the time over which it is given When treatment is given by means of a mold that can be removed and reapplied daily there is no difficulty and a fractionated treatment can be extended over any number of days just as in the case of x rays With implanted radium, however a free choice of time is restricted but the element of time in implant dosage remains as important as the number of roentgens delivered

Functions of a Dosage System

With any assemblage of radium intended for the treatment of a tumor the dose de livered will obviously depend on the amount of radium present its filtration the duration of application the area or volume covered and in many cases the distance between tumor and radium In addition to obtain as homo geneous irradiation as possible the distribu tion and number of the radium sources must be considered

The Paterson Parker system of expressing radium dose has been found to be most gen erally useful in practice [8 10] and examples of its application will be given The necessary tables and rules have been published and will be found in the references given Similar tables by E H Quimby [12] are also avail able

In every case the therapist must first come to three decisions (1) the appropriate type of treatment which is a clinical matter (2) the size of the tumor or the physical extent of the necessary treatment which is a matter of measurement (3) the dose required which is a matter of biology

These decisions having been made the dosage system answers two questions (1) how much radium to use (2) how to dis tribute it The fact that the answer is given in milligram hours per 1,000 r sometimes causes confusion but as the time will already have been decided by the statement of dose re quired the necessary milligrams can be de duced The convenience of this method is best illustrated by two examples

1 By reference to the dosage system it is found that a certain implant requires 2 740 mgh to deliver the required dose but it has been decided to deliver the dose in 200 hours therefore 13 7 mg of radium are required In practice however radium is available in in tegral units in this case it might be that a satisfactory implant could be constructed with either 12 mg or 14 mg As 13 7 mg is ideal

TABLE 21 1 —MILLIGRAM HOURS OF INTERSTITIAL RADIATION NECESSARY TO DELIVER 1 000 ROENTGENS IN VARIOUS VOLUMES

(Filter 0 5 mm Pt)

Volume (cc)	*Mgh for 1000 r*	*Diameter of sphere (cm)*	*Mgh for 1000 r*
5	200	1 0	40
10	320	1 5	100
15	390	2 0	180
20	440	2 5	280
30	540	3 0	390
40	620	3 5	475
60	750	4 0	575
80	870	4 5	675
100	1000	5 0	790
125	1120	6 0	1070
150	1250	7 0	1400
175	1390		
200	1500		
250	1680		
300	1800		

SOURCE O Glasser F H Quimby L S Taylor and J L Weatherwax *Physical Foundations of Radiology* 2nd ed New York Paul B Hoeber Inc 1952 p 366 (*Courtesy* authors and publisher)

the nearest choice available is 14 mg Using now 14 mg the time for the original required dose becomes 2 740 — 14 or 195 5 hours to the nearest half hour

2 In the case of a mold it is found that 3 650 mgh are required to deliver the required dose It has been convenient to load the mold with 63 mg of radium The time therefore is 58 hours If however it is desired to give the dose over a period of 8 days the mold will be worn daily for 58 — 8 or 7 25 hours daily

In this way the therapist is left as free as possible both to choose the conditions of treatment and to make the best use of his radium in observing the distribution rules i e, he is not tied to an exact amount of radium but is guided to a figure to which he must approximate The actual amount of radium he does use then decides the exact time of application

Radium containers whether tubes or needles can be arranged in only a limited number of ways Implants take the form of one or two planes of radium or that rational form of pincushioning called the volume implant point sources lines and planes are used in intracavitary methods and planes rings and cylinders are the usual forms of molds The dosage tables are equally applicable to all these patterns but it will be more convenient to treat the three main methods separately starting with needle implants because they are more widely used

IMPLANTED RADIUM

The Single Plane Implant

The single plane of multitudinous applications perhaps deserves to be called the classical implant As an example it will serve to illustrate most of the considerations that enter into the design of a treatment

An epithelioma of 3 cm diameter lying in a flat area of skin such as the cheek will be considered The three decisions mentioned have been arrived at as follows First that it can be adequately covered in area and depth by a single plane implant in other words as there will be no difficulty in treating a sufficient area it has been decided that 1 cm of thickness will result in a sufficient depth of treatment As for dose 6 500 r in 6 5 days represents a reasonable decision (it is not suggested as an invariable standard) Last the area to be treated must be decided and that is partly determined by the needles to be used At this stage one has a general idea of the implant as an outline of radium well wide of the lesion with a number of needles crossing the area at about 1 cm spacing The tumor being of 3 cm diameter a simple way of treating it will be to build round it a square implant of 5 cm side using needles of 4 5 cm active length (the total length of these needles is 6 cm) In this way we finally arrive at the area to be treated 25 sq cm

Turning now to the dosage tables we find that at 0 5 cm from a plane of 25 sq cm 1 000 r is delivered by 429 mgh This is the only use we make of the tables We proceed as follows

1 000 r given by 429 mgh
6,500 r given by 2 790 mgh
6 5 days=156 hours 2 790—156=17 8 mg

We now have to see how closely this figure of 17 8 mg can be approached in building up our implant with the needles available The implant cannot exist until it is outlined therefore the first step is to specify the bounding needles four 3 mg needles arranged in a square of side 5 cm The boundary has used up 12 mg leaving about 6 mg to be distributed over the area Four 1 5 mg needles

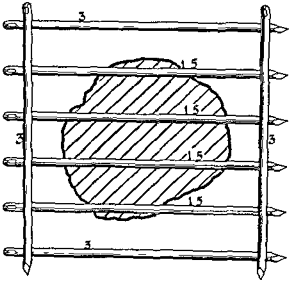


Fig 21 1 Diagram of implant as intended Shaded area represents the tumor The generous margin around its apparent edge is deliberate and important With this arrangement of needles the whole area is treated to an effectively uniform dose

In x ray therapy and in gamma ray therapy it is the invariable practice to relate the dose given with the time over which it is given. When treatment is given by means of a mold that can be removed and reapplied daily there is no difficulty, and a fractionated treatment can be extended over any number of days just as in the case of x rays. With implanted radium, however, a free choice of time is restricted, but the element of time in implant dosage remains as important as the number of roentgens delivered.

Functions of a Dosage System

With any assemblage of radium intended for the treatment of a tumor, the dose delivered will obviously depend on the amount of radium present, its filtration, the duration of application, the area or volume covered, and in many cases the distance between tumor and radium. In addition, to obtain as homogeneous irradiation as possible, the distribution and number of the radium sources must be considered.

The Paterson-Parker system of expressing radium dose has been found to be most generally useful in practice [8-10] and examples of its application will be given. The necessary tables and rules have been published and will be found in the references given. Similar tables by E. H. Quimby [12] are also available.

In every case the therapist must first come to three decisions: (1) the appropriate type of treatment, which is a clinical matter; (2) the size of the tumor, or the physical extent of the necessary treatment, which is a matter of measurement; (3) the dose required, which is a matter of biology.

These decisions having been made, the dosage system answers two questions: (1) how much radium to use; (2) how to distribute it. The fact that the answer is given in milligram hours per 1,000 r sometimes causes confusion, but, as the time will already have been decided by the statement of dose required, the necessary milligrams can be deduced. The convenience of this method is best illustrated by two examples.

1. By reference to the dosage system it is found that a certain implant requires 2,740 mgh to deliver the required dose, but it has been decided to deliver the dose in 200 hours; therefore 13.7 mg of radium are required. In practice, however, radium is available in integral units; in this case it might be that a satisfactory implant could be constructed with either 12 mg or 14 mg. As 13.7 mg is ideal

TABLE 21.1.—Milligram Hours of Interstitial Radiation Necessary to Deliver 1,000 Roentgens in Various Volumes

(Filter 0.5 mm Pt)

Volume (cc.)	*Mgh for 1000 r*	*Diameter of sphere (cm.)*	*Mgh for 1000 r*
5	200	1.0	40
10	320	1.5	100
15	390	2.0	180
20	440	2.5	280
30	540	3.0	390
40	620	3.5	475
60	750	4.0	575
80	870	4.5	675
100	1000	5.0	790
125	1120	6.0	1070
150	1250	7.0	1400
175	1390		
200	1500		
250	1680		
300	1800		

Source: O. Glasser, E. H. Quimby, L. S. Taylor and J. L. Weatherwax, *Physical Foundations of Radiology*, 2nd ed., New York, Paul B. Hoeber, Inc., 1952, p. 366. (*Courtesy* authors and publisher.)

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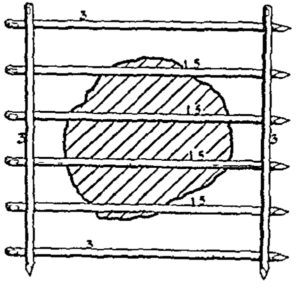


Fig 21 1 Diagram of implant as intended Shaded area represents the tumor The generous margin around its apparent edge is deliberate and important With this arrangement of needles the whole area is treated to an effectively uniform dose

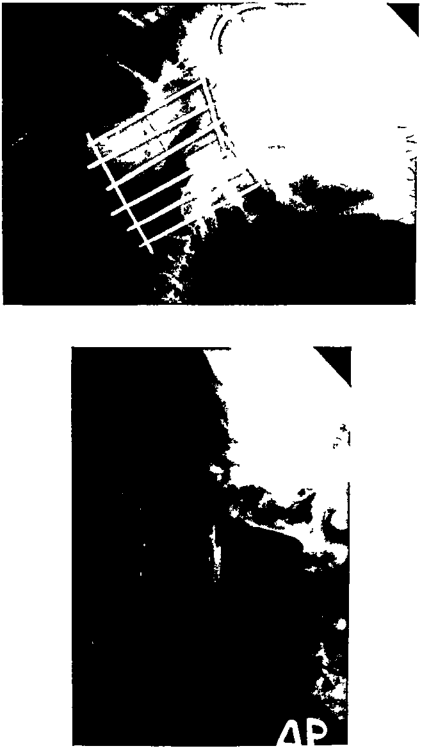


Fig 21 2 Radiographs of implant as performed Anteroposterior and lateral views are required for the measurement of area The ring is a magnification gauge

will supply the right amount and as they have the same dimensions as the 3 mg needles they will divide the area into five strips 1 cm wide as shown at Figure 21 1 The spacing is satis factory while the distribution rule for an implant of this size requires two thirds of the radium round the boundary and one third dis tributed over the area which is exactly what we have

The preliminary work is now complete and with Figure 21 1 in mind the implant is per formed A sterilized metal ruler is used to check measurements but in the performance it is of course quite essential to concentrate on the tumor under one s hand and not on a diagram on paper

As finally performed and as illustrated by the radiograph Figure 21 2 there has been one last consideration based on anatomy The implant is partly on the mandible and partly on the neck In order to follow the contour of the skin surface more easily the posterior needle of the original diagram has been re placed by two shorter ones They have an active length of 2 cm and therefore contain 1 33 mg of radium

When the implant is completed its measure ments are checked and these measurements allow one to arrive at a provisional time

The next step is always to discover by means of radiography the dimensions of the implant as actually performed Figure 21 2 shows the usual pair of perpendicular views the metal ring serving as a magnification gauge From a study of the films the physicist arrives at the area of the implant and hence the corrected time to deliver the dose that has been speci fied by the therapist At the same time any physical defects are noted and any necessary remedy of them is discussed In the example which shows a good standard of performance the area was assessed at 27 sq cm and 17 6 mg of radium were used A fresh calculation exactly in the manner shown on page 357 resulted in a corrected time of 171 hours for a dose of 6 500 r at 0 5 cm

Assessment of Dose

Tissue in contact with a radium needle necessarily receives dosage at a high and un ascertainable rate Moreover presumably be cause of the small volume of tissue concerned there is no clinical evidence of this localized high dose It becomes necessary therefore to adopt a method of stating dose that can be related to visible effects In practice it has been found that if doses are calculated at 0 5 cm from an implanted plane of radium the effects are comparable with the same dose delivered by a superficial applicator This is the usual method of stating implant dosage and no single plane implant is expected within the ordinary meaning of tissue tolerance to treat a greater thickness of tissue than 0 5 cm on each side of itself Some exceptions will be noticed later

Although the efficacy of radium treatment lies in its action at a distance it is always necessary to remember how rapidly this action is diminished by distance the idea that dom inates the planning of all brachyradium treat ments For this purpose the implications of Figure 21 3 must be fixed in the mind It shows the rate at which dosage from a small plane of radium falls as a consequence of increasing

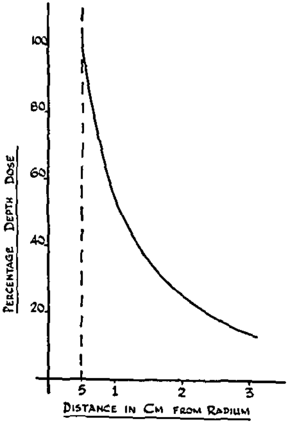


Fig 21 3 The rap d rate of fall of dose from a plane of radium of 20 sq cm The dose at 0 5 cm from the plane is taken as 100 per cent

distance only Absorption is ignored, as it usually is in radium therapy

Doses suggested in this chapter are generalizations only each case calls for its own decision

Effect of Needle Loading

Because implants result in continuous treatment the strength of the available sources has important consequences Conversely if radon or isotope sources are to be made up for individual cases there is an optimum activity that may be prescribed The argument runs as follows to insure homogeneous irradiation a certain spacing between needles must not be exceeded therefore a certain minimum number of needles at least must be implanted therefore depending on the strength of the needles there is a minimum total of radium possible in a given case The total amount of radium determines the dose rate and the dose rate determines the time at which tumor lethal dose is reached

For example an implant using the minimum number of needles might give 7 000 r in 7 days but if needles twice as strong were alone available the same figure of 7 000 r would now be reached in 3 5 days which is certainly a different and excessive dose

It is clear therefore that the key to an implant is its dose rate and that this if high may require a departure from the traditional over all time of 6 to 10 days

British Standard Loading

Linear loading rates of 0 66 mg and 0 33 mg per cm of active length have been used for many years and since 1948 have been standardized for needles issued by the Ministry of Health for the National Health Service These needles have been found convenient for implant work at a dose rate of about 1 000 r per day when used according to the Paterson Parker rules A summary of the most useful sizes is given in Table 21 2 They have been assumed in the previous example

Applications of Implants

In all cases where any implant is proposed examination of the patient must include a careful scrutiny to make sure that an ample margin (about 1 cm) of healthy tissue is available all around the tumor to receive the peripheral needles of the implant and open ended implants must pass beyond the tumor even more generously

Selection of the appropriate implant depends chiefly on the shape of the tumor or the form of the implant that will best fit round it with the peripheral needles in uninvaded

Fig 21 4 Needle implant after radical mastectomy The axilla has also been implanted

TABLE 21 2—TABLE OF COMMONLY USED RADIUM NEEDLES

Total mg at 0 66 mg per cm	3	2	1 3*	1
Total mg at 0 33 mg per cm	1 5	1	0 66*	0 5
Active length cm	4 5	3	2	1 5
Total length cm	5 8	4 2	3 5	2 5
Screen mm of Pt	0 65	0 6	0 6	0 6

NOTE All are British standard needles except those marked with an asterisk which are also of standard linear loading Eight needles in four pairs are represented

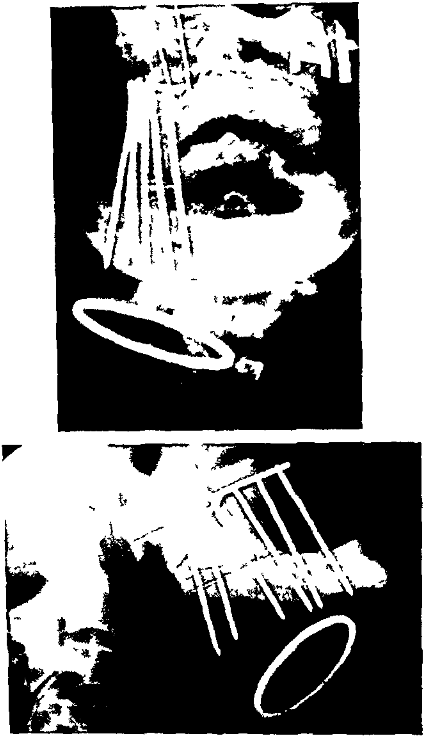


Fig 21 5 Single-plane needle implants in side of tongue

tissue It is necessary to be clear beforehand what is intended and to execute the design as closely as possible There are two reasons for the strict observance of geometry first rules apply to the conditions specified and second intelligible radiographs are required for a final calculation of dose rate The arithmetic of other types of implant follows the same arguments as the example just given and they are similarly provided for in the tables of the dosage system

SINGLE PLANE IMPLANT

Single plane implants are always possible for the many small skin cancers more usually treated for convenience by x rays in one or

a few applications As the area to be treated increases however the argument in favor of implant becomes stronger for now the alternative is a fractionated course of x ray treatments and in any case, the risks of high dosage are less For instance very large single plane implants illustrated in Figure 21 4 are commonly used for recurrent carcinoma after radical amputation of the breast giving a dose of 5,500 r in 6 days over an area of some 300 sq cm and these implants are well tolerated

not invade deeply A single plane implant through the base of such a growth is adequate treatment although the external bulk of it will receive only a negligible dose

Dose

At a rate of 1 000 r per day a plane implant in the skin or mouth 15 sq cm in area will tolerate 6 000 r easily although an acute reaction will be produced At the same rate and area 7 000 r could be tolerated and 4 500 r would not result in many cures The

Fig 21 6 Two plane needle implants of anus

In the mouth probably more than half the occurring cancers are suitable for this method These are ulcers on the buccal surfaces and the dorsum and sides of the tongue The typical side of tongue implant is usually carried out in needles of active length 3 cm (containing therefore 2 or 1 mg) implanted vertically in the manner of Figure 21 5

The lip is another suitable site particularly if the length of lip involved or wide infiltration renders the tumor less suitable for mold treatment

There is a type of exuberant skin cancer that forms a large projecting tumor but does

smaller the area treated the more safely may a high dose be given

TWO PLANE IMPLANT

A two plane implant treats a slab of tissue more than 1 cm thick It should not be used beyond a thickness of 2 5 cm i e two planar implants not more than 2 5 cm apart themselves being clear of the limits of the tumor include the whole lesion between them

These conditions limit the field of this pattern of implant to a few typical sites side of tongue fauces anus and vulva

In the tongue with its free margin it is

impossible for the lateral plane to be clear of tumor at any rate the needles should be as superficial as possible and on occasion when the tumorous edge of the tongue is too friable to hold needles they can be held in a thin sheet of sponge rubber stitched to the floor of the mouth and the cheek

In designing small two plane implants for the tongue it will be found that the necessary amount of radium is contained in too few needles of usual strength to allow of a reasonably sufficient number of sources to obey distribution rules Such cases (and also the smallest volume implants) are occasions when radon or isotope sources of precalculated activity would have advantages

Implants of the anus and vulva often call for the use of needles having an active length of 4 5 cm (i e , 3 and 1 5 mg) An example is shown in Figure 21 6 The needles are inserted with the patient in the lithotomy position and some care is required to make allowance for the effect of restoring the parts to the normal position

The preservation of function is the great advantage to be expected from the anal implant Contrary to the usual expectation a preliminary colostomy is not necessary if the bowel is first cleared and then constipated by opiates and a nonresidue diet the six days required for the treatment can nearly always be secured without a motion and in any case failure in this respect is not disastrous

Dose

The allowable separation between the planes is not great even with a separation of 2 cm the minimum dose between them drops to about 80 per cent of the dose received at points 0 5 cm from the inner aspect of each plane The dose received at this plane 0 5 cm inside each radium plane is used to express the dose administered by the implant Tolerated doses run parallel with single plane dosage except that perineal tolerance is notoriously bad and in this situation the lower ranges of dosage should not be exceeded without good reason

VOLUME IMPLANT

The implant is so called because it is used when the tumor cannot be segregated on one plane or between two planes of treated tissue but occupies a volume of similar diameter in all directions In practice as the volume must be defined by needles it takes the form of a cylinder of circular or elliptical section with one or both ends closed by crossing needles In the tongue the usual needles are again the 1 mg needles of active length 3 cm

Its field of usefulness is principally the tongue for those tumors that are not suitable for a single plane—the two plane type being a small intermediate group At the anus and vulva however it is less often to be preferred Secondary metastases to regional nodes particularly in the axilla can be treated and occasionally tumors of the breast itself An example in the tongue is shown in Figure 21 7

Dose

In the tongue the common cylindrical implant has a mean diameter of about 3 5 cm but may well be larger In recognition of the greater volume of tissue subjected to it the dose is seldom carried to the upper figures usual for single planes An average figure would be 6 500 r in 6 5 days

RADON IMPLANTS

It is perfectly possible to replace *radium* by radon in all forms of radium work and by this means seeds needles or strong tubes can be prepared for special cases Although the treatment is necessarily given at a falling dose rate (half life 3 8 days) no effects different from those of a radium implant are detectable clinically when similar doses are given in the same over all time This seems to be true also of permanent radon implants in which 77 per cent of the dose is delivered within the first eight days

The use of radon in seeds however is a separate contribution to therapeutics for three reasons they are small and therefore can be applied to highly curved or inaccessible surfaces they decay to inactivity and are of small intrinsic value and therefore may be left *in situ* and be used for outpatients

The seed consists of a metal capillary about 4 mm long with a wall thickness of 0 5 *mm* of gold or the equivalent in other *noncorroding* metal They may be had in threaded

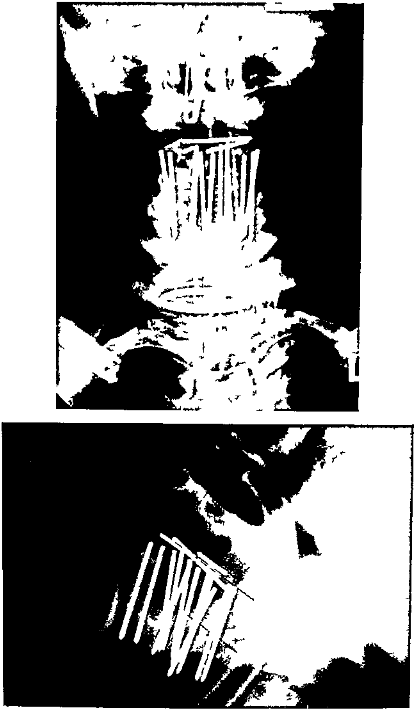


Fig 21 7 Volume needle implants of tongue

sheaths but of course are not threaded if a permanent implant is intended At the time of implant they should contain 0 7 to 1 mc and must be measured individually

Gold Radon Seed Implants

In the past many attempts have been made to exploit the use of radon seeds by endoscopic methods for example in carcinoma of the esophagus but accurate work is impossible and probably this approach has been abandoned almost entirely

The regions where small sources are advantageous are the inner canthus of the eye the fauces the soft palate and the mucoperiosteum of the gums and hard palate—for some small cancers in these regions there is no good substitute for a seed implant Exam

Fig 21 10 Gold radon seeds in the soft palate and fauces

thickness of tissue than 1 cm The tumor is exposed by suprapubic cystotomy and all exuberant tissue removed by electrocoagulation until a clear view of the tumor base and a measurement of its area are obtained This area with a margin of about 1 cm all round is then implanted according to the usual rules and the bladder is closed An indwelling catheter is left in place for 5 days The usual radiographs are required for dose assessment (Figure 21 12) A number of authors have published details of this form of treatment [2 3 11]

Dosage with Radon Seeds

Even when implanting with radon in removable needles it is necessary to be accurate in the amount used because the falling dose

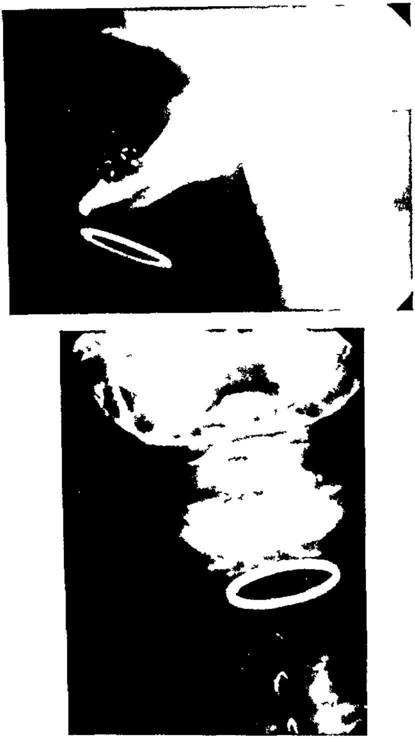


Fig 21 11 Gold radon seeds in the floor of mo th a d alveolo r dges

rate may make it impossible to achieve the d sired dose by any p olongation of time In the case of a permanent s ed implant accuracy in theory must be absolu e be ause the do e given is inevitably that resulting from the to al decay of the rad m implan ed

I tunately m nt seed implants are sm l and capable of t e a ne some a cilen al excess but recognizing that overdosage rather than underdosage is the commoner fault the operator is well advised to aim at a lower dose than the maximum he would consider in any given case if radio raphic measurement then shows that too l w a d se resulted the defect can be made good by a small x ray contribu tion

Dose levels are those of radium implants areas of about 4 cm sq will tolerate up to 8 000 r and doses below 5 000 r will probably be ineffective in many cases

Seeds stronger than 1 mc each are often recommended but are not desirable They produce small spheres of excessive dosage around themselves that may necrose, and they result in too few sources in the implant to give good dose distribution A larger number of weak radon seeds makes for more uniform dosage

Contraindications to Implants

Certain areas of skin are well known to have poor tolerance chiefly the skin of the limbs and particularly of hands and feet In all these sites the radiotherapist will prefer the gentlest means of delivering any given dose, that is to say a surface applicator Although the stated dose may be the same there is a difference in the manner of administration between implants and external methods The stated implant dose is a minimum and areas of much higher dose exist in the immediate proximity of the needles moreover it is the minimum created within a volume of tissue In the case of external irradiation the stated dose is maximum and applies only to a surface

The hazard of bone and particularly mandibular necrosis is well recognized A needle laid in contact with bone in the course of a normal implant is probably always harmless danger arises when needles are arranged to include bone between them It is best therefore to avoid including the mandible within a two-plane or volume implant in spite of the strong temptation to do so offered by many cancers in the anterior part of the mouth and for which a radium mold is often a more suitable alternative

INTRACAVITARY RADIUM THERAPY

The methods of implant so far described have all (even the single plane) been designed with the idea of placing some of the radium beyond the limits of the tumor and thus marking out an area or volume to be irradiated as evenly as possible

The contrasting intracavitary method of lumping all the radium centrally and treating centrifugally has important applications Because of the inevitable excessive dose inside the limits to which the desired working dose is thrown, it is not in itself a method of choice and is used where methods of homogeneous dosage are impracticable and where, as a rule, the central radium is surrounded either by massive tumor or by a space occupying material, such as sponge rubber filling a cavity

The central radium need not always take the form of a single source and does not do so in the most important example of intracavitary treatment—treatment of the body and neck of the uterus

The many different uterine and vaginal applicators all result in surface doses of the order of 20 000 r but a better way of stating the effective dose delivered is to estimate it at some defined point in the paracervical tissue In this way an estimate of dosage as it affects a substantial volume of tissue can be formed and the limit of tolerance defined Analysis of treated cases [15] has shown that signs of high dose effects are frequent if a dose of 8 000 r in a period of 10 days is exceeded at a point 2 cm lateral to the mid line in the paracervical triangle

The statement of dosage therefore is only true at some arbitrary point and is not a tumor dose after the usage of other methods Its use is merely to define tolerance and allow of the repetition and comparison of similar treatments

Various other hollow organs such as the esophagus and rectum have been extensively treated by linear sources placed within them, but with little success and the only other site where at present intracavitary radium is frequently used is in the nose and its associated sinuses After surgical exenteration of the tumor the resulting cavity may be irradiated by a central source held in a mass of sponge rubber or in a fitted applicator but it is often possible and perhaps desirable to dispense with the surgical preparation and simply use the tumor mass itself to support a central tube in the radium tube An example of a central tube in the maxillary sinus is shown in Figure 21 13 Such a treatment is controlled by an estimate of the radius of the sphere that will certainly contain all the tumor The treatment is then

calculated to deliver at least the desired tumor dose at this distance In practice it is found that a dose of 8 000 r in about 10 days may be taken at 2 cm from a tube in the maxillary sinus although that is probably an upper limit of dosage and is not called for in most cases

Spherical irradiation from a single source may be inappropriate in shape and just as in the case of the uterine cervix better cover may result from two or more central foci The intracavitary technic may thus be developed into central high dose planar implants at say, 0 5 cm off the surface of the applicator is the one to be regarded as a true tissue dose rather than the surface dose itself

RADIUM MOLDS

The manufacture of radium molds is laborious and perhaps not always very successful without trained assistance and for this reason superficial radium therapy is not used to the extent its possibilities justify None the less molds are an important contribution to the full range of method and for some sites may well be considered indispensable It is also true that once the equipment is established plenty of good if not absolutely necessary indications are found for its use

Fig 21 12 Radon seed implant of the trigone of the urinary bladder

They have not been found a good substitute for orthodox implants but have occasional applications In the nose and ethmoid sinuses for example a dose of 6 000 r in the usual time at 1 cm from a plane implant of suitable strength is well tolerated and results in the effective treatment of a slab of tissue 2 cm thick

In general intracavitary methods are used for the lack of a more inclusive plan of attack from without inward Excessive doses are bound to be taken and even if the radium is contained within an inert applicator the dose

The chief merits of molds are probably (1) the absence of local high dose areas or in some double molds an approach to homogeneous dosage (2) the deliberation with which each treatment is designed and (3) the precision with which the desired dose is administered both in amount and position

Great variety is possible in the construction of molds but always with the same essentials

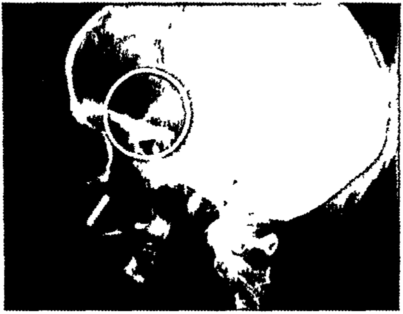


Fig 21 13 A common intracavitary method a 25 mg radium tube placed in the middle of a tumor filled antrum

in view Except when fixed to the skin adhesively for continuous application a mold must be removable with ease and replaceable with certainty it must be so closely adapted to the part treated that relative movement is if not impossible at least avoidable by simple supervision it must be comfortable enough to be worn without resentment for hours on end

After these requirements of fit and fixture comes the radium bearing area itself Provision must be made for holding the radium at a definite measured distance from the surface to be treated and the radium tubes must be held securely in predetermined distribution

An equipment of materials is required for taking impressions for making models and for making the mold as it is to be worn New materials various forms of methyl methacrylate and cellulose acetate and polyvinyl chloride as described by Hunnings have been added to those described by Paterson and MacVicar and Melville, but the various stages of mold making remain unchanged The main point is that the materials should be easy to cut shape and fix together stable at body temperature and impervious to saliva and discharge if exposed to them It is sometimes recommended particularly in intraoral molds that lead be incorporated to screen the radium in unwanted directions In fact to be of value the lead must be impracticably thick and the best protection is distance provided by designing the mold to prevent the near approach to the radium of everything but the surface to be treated (See Volume III Chapter 26)

A necessary part of the equipment is of course a sufficiency of radium sources in convenient units the usual difficulty being lack of sufficient strong tubes for the larger molds and of small tubes to fit the highly curved molds intended to be worn in the mouth To illustrate the amounts required Table 21 3 shows the milligrams required for a selection of areas and treating distances An idea of the depth dose properties of small single molds may be gathered from Table 21 4 which shows a fall in dose to 50 per cent in about the first centimeter below the surface

Applications of Molds

Molds may be constructed to treat nearly any superficial cancer, but there are some special applications for which there is no good substitute and which should be within the scope of every radiotherapeutic center These are all in sites of poor radiation tolerance and will be briefly illustrated There is one contraindication even among superficial tumors and that is ulceration in a recessive angle such as occurs at the junction of nostril and cheek and ear and scalp A mold convex to the point of angularity cannot be trusted to treat a sufficient depth but convex surfaces treated therefore by a concave mold are favorable in this respect

Perhaps the commonest indication for a mold is cancer affecting the limbs and especially the hands and feet In the same category come molds for areas so large that treatment by other methods would impose serious limitations of dose but where a limited depth dose can be accepted Such areas of ulceration occur on the scalp and trunk but the most frequent example is the treatment of skin nodules after a radical mastectomy that has left little but skin covering the ribs For this purpose the radium in needles is distributed on a mold 1 5 cm thick built up of

TABLE 21 3 —THE AMOUNT OF RADIUM IN MILLIGRAMS REQUIRED ON MOLDS TO DELIVER 6 500 R IN 100 HOURS FOR VARIOUS AREAS AND TREATING DISTANCES

	Distance			
Area	*0 5 cm*	*1 cm*	*2 cm*	*3 cm*
10 cm*	18	33	72	120
20 cm	29	50	93	152
40 cm	46	75	132	199

TABLE 21-4 —PERCENTAGE DEPTH DOSES FROM A MOLD 20CM AT VARIOUS TREATING DISTANCES

	Distance			
Depth	*0.5 cm*	*1 cm*	*1.5 cm*	*2 cm*
Surface	100	100	100	100
0 5 cm	55	72	75	77
1 cm	40	54	58	61

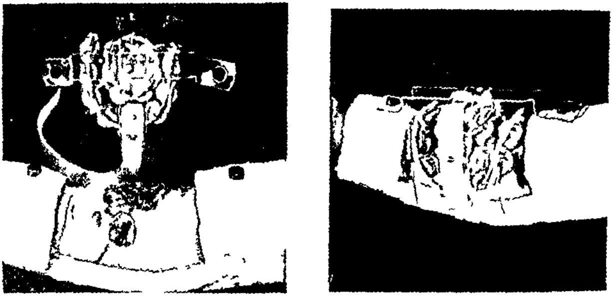


Fig 21 14 A tumor of the arm treated by radium mold (Figures 21 14 through 21 19 show a variety of tumors preferably treated by molds Various forms of construction are used for the molds)

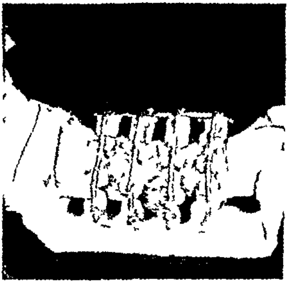


Fig 21 15 A tumor of the forearm treated by radium mold

Fig 21 16 A tumor of the hand treated by rad um mold

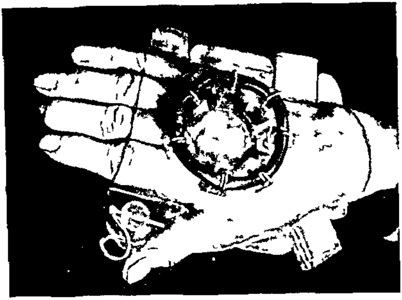
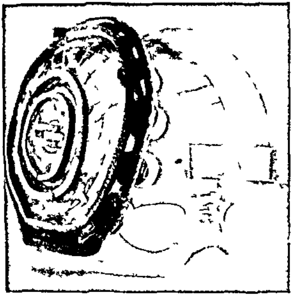


Fig 21 17 A tumor of the hand treated by a Lucite radium mold

Fig 21 18 A tumor of the foot treated by radium mold



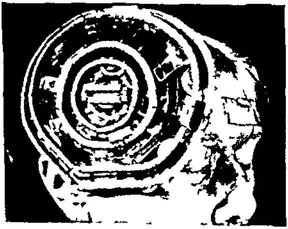


Fig 21 19 A basal-cell carcinoma of the scalp being treated by radium mold

Fig 21 20 Mold treatment after radical mastectomy

sheets of felt of which one surface is adhesive and whose lower layer is stuck to the chest wall Felt of this kind is regularly used in orthopedics Some examples of these molds are shown in Figures 21 14 to 21 20

In other sites where depth dose is important, double molds are used consisting of two opposed molds including the tissue to be treated between them Ulceration encroaching on the anterior half of the mandible is a strong indication for a mold of this type the cancer usually taking origin on the cheek or floor of the mouth Tissue masses up to 3 5 cm thick are usefully treatable by this method The inner mold made of dental tray compound treats at 0 5 cm from the mucosal surface and is otherwise made as bulky as the mouth will permit in order to keep everything except the treated surface as far from the radium as possible The contribution of the outer mold at 2 cm from the skin is intended to improve the depth dose of the inner one The arrangement is illustrated in Figure 21 21

Another part of notoriously poor tolerance is the penis It may be treated with safety by means of a cylindrical mold consisting of an arrangement of rings of radium concentric with and at a determined distance from an inner cylinder containing the penis One design is illustrated in Figure 21 22 and consists of an inner cylinder to hold the penis over

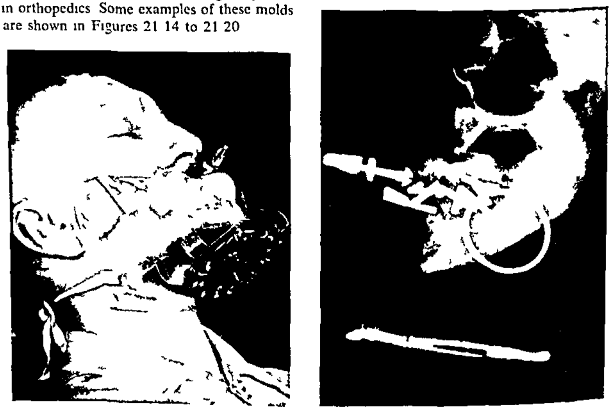


Fig 21 21 Double mold to treat the floor of mouth with a radiograph to show the disposition of the radium

which is to be placed the coaxial outer cylinder loaded with radium The length of the active cylinder is commonly 8 cm and the diameter of the radium rings 4 cm more than the inner cylinder The minimum axial dose is then 90 per cent of the dose on the inner cylinder which may be 6 000 r in 8 days To avoid

Fig 21 22 Cylindrical mold for the penis The larger cyl nder carry ng the radium will be placed over th smaller one already in pos tion

an uncomfortably long wearing time per day relatively large amounts of radium are re quired in the conditions just given a daily application of about 12 hours is required with a total radium loading of about 160 mg

There are other sites where molds are fre quently employed if perhaps less essentially The double mold for the lower lip Figure

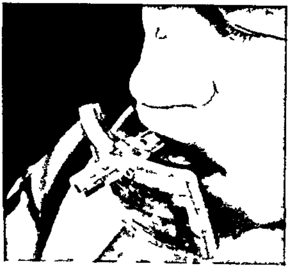
Fig 21 24 Double mold for the auricle

21 23 is the commonest example in this cate gory Lips can be treated in other ways but there is statistical evidence slightly in favor of molds—78 per cent five year crude survival rate compared with 70 per cent for the x ray treatment of similar cases

As a last example of a site preferentially treated by a mold Figure 21 24 shows a double mold for carcinoma of the auricle By this means the incidence of late cartilage necrosis is almost entirely avoided

Mold Dosage

The important distinction between implants and molds in the implications of the stated



F g 21 23 Double l p mold The l er plane of rad um is conta ned in the intraoral block

dose has already been mentioned It is for this reason that doses of 5 500 r in 8 days may be given to fingers, and for the same reason areas of good tolerance, such as the buccal mucosa, may be given surface doses up to 8 000 r when depth effect is desired There is therefore a range of dosage between these figures depending on site area importance of depth effect and in the case of double molds the separation of the radium planes

Measurement of Dose

The dose rate of molds is usually the rate calculated according to the Paterson Parker tables but the method lends itself to direct measurement with ionization chambers and obviously this refinement should be practiced whenever possible

Radon Molds

Where seeds are available a very convenient application for them is in outpatient molds For any small skin tumors these may replace single x ray treatments with better cosmetic effects and of course can be applied to the skin in those sites of poor tolerance

The adhesive orthopedic felt already mentioned is used in one or more thicknesses of 0 5 cm and a measured area on its upper surface is appropriately loaded with seeds to deliver the desired dose in seven to eight days continuous application The seeds are held in place under a cover of adhesive tape Projecting tumors are accommodated in a cavity built up with felt rings The adhesion of the mold is reinforced by an over all covering of elastic adhesive tape

Contact Molds

In the case of a needle or seed implant calculations are made on the basis of an intended dose at 0 5 cm from the implant In the case of a continuous mold at 0 5 cm from the skin exactly the same radium is used but removed from the skin by 0 5 cm with consequently much less effective treatment of the first subcutaneous centimeter In theory it makes no difference to epidermal tolerance whether the radium is below the surface or above it and therefore one is at liberty to use radium as if for an implant either on the surface or at a distance smaller than 0 5 cm above it In practice it has been found safer not to have the sources quite in contact with the skin This possibility and the use of gold seeds are sometimes of advantage where for some reason, it is desired to avoid an implant, or where even a gold seed implant might be difficult For example a small carcinoma in the hollow of the ear may be treated with a contact mold made in the following way a suitable mass of softened impression compound is pressed onto the tumor and molded to the anatomic detail of the pinna It is allowed to harden and when removed in area surrounding the tumor is outlined and measured The area on the mold is now implanted with gold seeds using heat to sink them just flush with the surface The mold positions itself with exactitude and needs only a light adhesive binding to keep it pressed home Implant loading for continuous application, is usually employed, but intermittent application can obviously be allowed for too

A Note on Dose Time Relationship

Throughout this chapter every statement of dose is accompanied by a time in which it is to be administered but in radium work this relationship is much disregarded although the dependence of effect on the over all period of an x ray treatment is of necessity always recognized

Implants must run their course at the rate of dosage computed as a rule from radiographic measurement of the implant as performed Suppose in a given case a dose of 6 000 r in 7 days was intended but by measurement it is determined that 6 000 r is given only after 8 days this dose has presumably a less effect Similarly if the intended dose rate is exceeded say 6 000 r in 5 days the dose has a greater effect

In order to achieve consistently the *same* effect from implants of varying dose rate there must exist some relationship between high rate implants of short duration and low rate implants of long duration Thus in the examples just given the equivalent of 6 000 r in 7 days might be taken at the lower rate as 7 000 r in 9 3 days and at the higher rate as 3 500 r in 2 9 days

The figures given are merely arithmetical examples and unfortunately there seems to

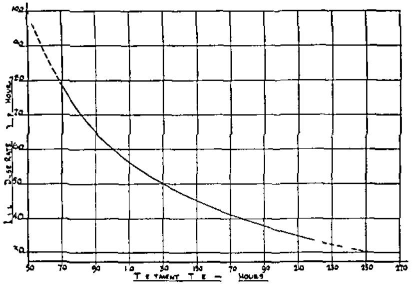


Fig 21 25 Dose rate Time curve to give dose equivalent to 7 000 r in 7 days for other treatment times For prescribed dose of R roentgens in 7 days and implant dose rate of x r/hr read required treatment time from curve opposite $\frac{7000}{R} \times$ r/hr

be no way of arriving at equivalent doses better than observation of many actual cases treated in varying conditions A review of this kind referring to x ray therapy has been published by Strandquist and Ahlbom The early experimental observations of MacWhirter and Ham on the disappearance dose for rodent ulcer under gamma ray treatment are highly relevant The curve shown in Figure 21 25 is one based on clinical data by Mr S K Stephenson of the physics department of the Christie Hospital and Holt Radium Institute and shows the connection between dose rate and time to produce the effect of 7 000 r in 7 days It must be repeated that this curve is entirely empiric and open to correction

So long as the effect desired is that of 7 000 r in 7 days the use of this curve is obvious the treatment time is read directly after the dose rate has been computed or dinarily by radiographic measurements Two doses therefore are recorded an actual dose of total roentgens in total time and an equivalent dose 7 000 r in 7 days in this case The curve is however also of avail when other doses are required once the habit has been formed of thinking of dose in roentgens within a fixed period for only by doing so can one be certain of graduating dosage according to one s intentions

Suppose a dose equivalent to R roentgens in 7 days is desired from an implant whose dose rate is found to be X r per hour it is required to find the time T for this implant to give the desired effect In Figure 21 26 the curve represents the standard iso effect graph for 7 000 r in 7 days X is the dose rate found for the implant and T is the unknown time for this implant to give the effect of R roentgens in 7 days The argument then runs —

At X r per hour TX roentgens in T hours

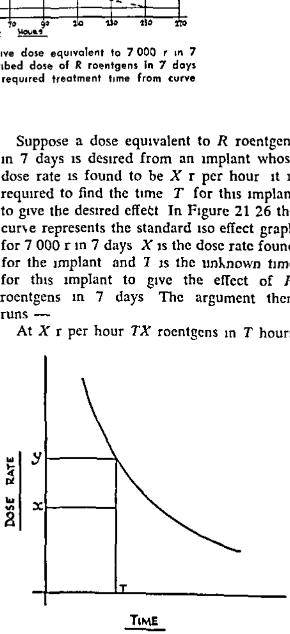


Fig 21 26 Standard iso-effect graph for 7 000 r in 7 days

are equivalent to R roentgens in 7 days

But at Y r per hour TY roentgens in T hours are equivalent to 7 000 r in 7 days

Assuming that the ratio of the equivalent 7 day doses is the same as the ratio of the actual doses in another fixed time, T, we can write

$$\frac{TX}{TY}=\frac{R}{7{,}000}$$

$$Y=\frac{7\,000}{R}Y$$

As X and R are known Y is found and applied to the standard curve to arrive at T

The actual dose will be TY roentgens in T hours equivalent to R roentgens in 7 days

It should now be clear that the method has two intentions to allow treatments at different dose rates to produce the same effect, and to allow control over graduated dosage at what ever rate it may be given The ordinary application has been described but other uses can be made of the iso effect curve of Figure 21 25, for example the assessment of total dosage accruing from separate parts of a complicated treatment and conversion to other equivalents than 7 day doses but these are beyond the scope of this chapter

CHAPTER 22

The Clinical Application of the Radium Element Pack

Constance A. P. Wood

The form of therapy known in America as treatment by the radium element pack or bomb has various names in other parts of the world. Thus in Great Britain it is known as radium beam therapy or teleradium treatment. In Sweden it is called treatment by radium cannon, while in France it is known as *telecurietherapie* and in Germany as *Radium fernbestralung*.

In this form of therapy the radium is placed at some distance from the patient, hence the term *tele*radium treatment. This form of therapy was developed chiefly during the third decade of the present century. The radium, commonly 3 to 10 Gm., is housed in a massive lead container with an aperture or window that restricts the rays emitted by the radium to a narrow beam which can be directed at a tumor in the same way as a beam of x rays.

APPARATUS

The radium element pack used by the author is described below. It was designed in the Radiotherapeutic Research Unit of the Medical Research Council of Great Britain. A general view of the apparatus is shown in Figure 22.1 and a sectional drawing of the treatment end is illustrated in Figure 22.2. The radium source* consists of 10 Gm. of radium sulphate contained in fifty 200 mg. monel metal tubes packed tightly inside a steel bobbin as shown in Figure 22.2 [6]. An important consideration in the design was the provision of increased protection for both patients and staff.

A novel feature of the unit was the pneumatic transference of the radium bobbin along a flexible metal pipe connecting the storage safe and the treatment end of the unit. When the radium is in the storage safe the radiation intensity throughout the treatment room is below the accepted maximum permissible value, the operator can enter the room with safety and set the patient in the correct position for treatment. After fixing the patient in position the operator can then withdraw to the observation room and move the radium bobbin into the treatment position by remote control. A clock, previously set to the required treatment time, starts running as soon as the radium arrives in position in the unit. The clock reaches zero when the requisite treatment time is completed and the radium is automatically blown back into the safe.

The use of tungsten alloy as protective material made a compact design possible. The absorption of gamma radiation by metals is directly proportional to their density. Lead with a density of 11.3 Gm./cc. has been the metal usually employed in making these units. Gold and platinum have occasionally been employed to make the nose piece of a teleradium unit but these metals are too costly to be used in the construction of the unit itself. Tungsten is the only other reasonably cheap metal that has a density comparable to that of gold. Tungsten, however, only attains this high density when it has been sintered at about

* In recent years, since radioactive cobalt has become available, cobalt has, in addition to its use in the larger telecurie units, been widely used to replace radium in many units of the type described above. Quantities of cobalt up to [illegible]000 curies can be used as the radioactive source in these units and the additional protection then required is obtained by the use of uranium instead of tungsten alloy as shielding material. A cobalt source of [illegible]000 curies enables the focal skin distance to be increased from 5.3 cm. to [illegible]0 or [illegible] cm., so considerably improving the depth dose (Chap. [illegible]).

3000°C and no means were available for heating masses of more than 100 lb to such a high temperature Experimentation led to the production and use of a nickel alloy of tungsten The density of this alloy is 16 5 Gm/cc which offers better protection than lead In addition further protection is afforded for the patient by the provision of a rotatable eccentric shield (Figure 22 2) which can be turned into the position giving the maximum protection during treatment

The suspension mechanism allows a vertical movement and rotation about a vertical and a horizontal axis Three interchangeable applicators—a 5-cm circle an 8 cm circle and a 6 × 8-cm rectangle—made of tungsten alloy and fitted to the head of the unit are used in treatment

The radium-skin distance is 8 3 cm and the filtration is equivalent to 1 5 mm Pt The measured isodose curves for the 5 cm circular applicator are shown in Figure 22 3

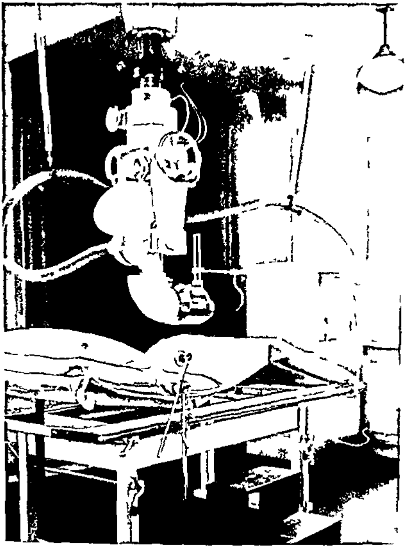


Fig 22 1 General view of 10 Gm radium beam unit This shows the flexible metal pipe through which the radium bobbin is transferred by pneumatic pressure between the storage safe and the head of the radium unit A treatment caliper is shown attached to the head of the unit

Protection

The unit is provided with stops limiting the angle through which it can be turned These stops insure that the primary beam is always directed toward two outside walls and prevent its ever being pointed toward adjacent occupied rooms (Figure 22 4) The observation room is separated from the treatment room by a 14 inch brick wall that reduces to a safe value any stray radiation from the unit or

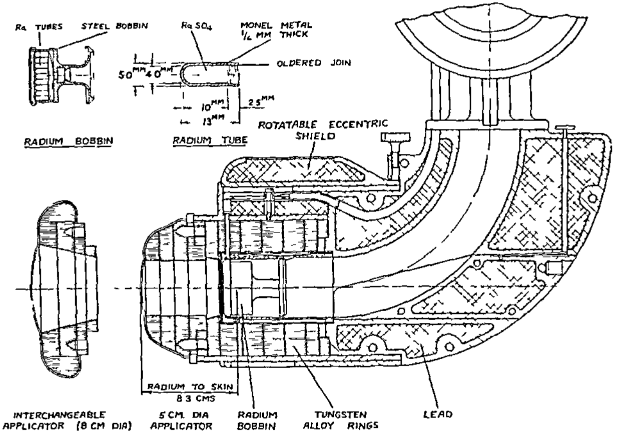


Fig 22 2 Cross section of head of radium beam unit

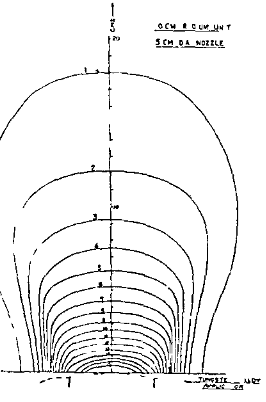


Fig 22-3 Isodose curves of 10 Gm radium beam unit with 5-cm diameter applicator

any scattered radiation from patient or couch A system of mirrors permits the operator to view the patient under treatment from the observation room The dose rate has been found to be constant and the total dose received by a typical radiographer over a period of twelve months working eight hours a day five days a week with this unit and an adjacent 200 kv x ray set was found to be only 6 r which was less than the accepted maximum permissible value this included the natural leak of the ionization chambers which would account for about 1 r per year The dose received during the same period by the radiotherapist who checked the settings of each patient was 3 r per year The complete safety for the personnel using this unit is manifest

The mean integral dose received by a group of approximately 200 patients undergoing radium beam treatment to the head and neck was found to be 10 7 megagram roentgens * which is considerably below the maximum

* The total energy absorbed in the patient's body during the treatment was measured by means of a life size model of the human body consisting of a large number of parallel plate ionization chambers each forming a section through the body [f]

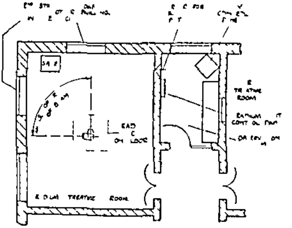


Fig 22-4 Plan of treatment room

integral dose which most patients can tolerate It may be stated therefore, that the constitutional effect of the radiation is rarely the limiting factor in radium beam treatment

TREATMENT

The technic of treatment described below is that initiated at the Medical Research Council Radiotherapeutic Research Unit London

Beam Direction

The rapidly falling depth dose and the small size of the fields used in teleradium treatment make accurate directioning of the beam extremely important A treatment caliper (Figure 22 5) is attached to the head of the unit It consists of two rigid arms—a vertical and a horizontal On the horizontal arm there is a movable arm and back pointer arranged so that the end of the pointer travels along the central axis of the radiation beam which is represented by a narrow pencil of light from a lamp and lens carried on the movable pointer Each field of treatment and the point of exit of the central ray of the beam for each

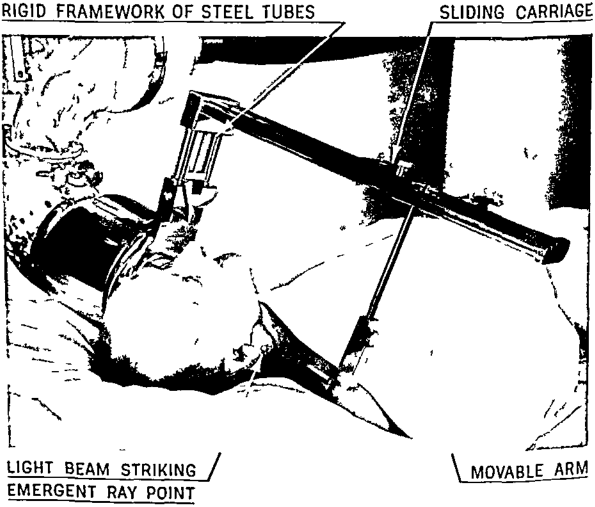


Fig 22 5 Treatment caliper attached to head of radium beam unit

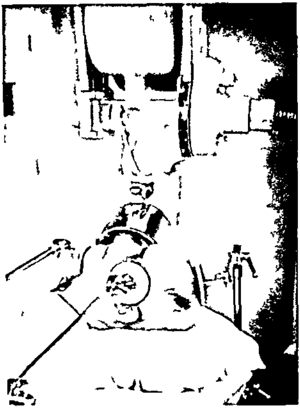


Fig 22-6 Method of stabilizing patient in position during treatment

field (i e , the emergent ray point) is marked on the patient s skin This emergent ray point is then defined by relating it to some bony anatomic landmark The emergent ray point is defined in this way for each field to be treated so that the direction of the beam can be repeated precisely at each treatment The patient is set up in position for treatment by bringing the field marked on his skin into contact with the corresponding mark on the applicator of the unit and then adjusting the angle of the radiation beam until the light spot on the patient from the movable pointer has been brought into coincidence with the emergent ray point marked on the patient Thus each successive treatment can be repeated with precision and the error in directing the beam by eye is eliminated

If the direction of the beam is to remain constant it is essential that the patient does not move throughout the course of treatment Hence the simple stabilizing device (Figure 22 6) consisting of a number of padded clamps on universal joints was utilized

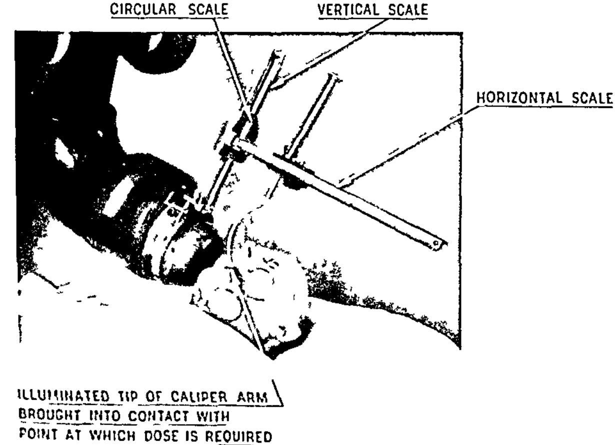


Fig 22-7 Measuring caliper mounted on wooden model of radium beam unit for point by point measurements on patients.

Measurement of Tumor Dose

The tumor dose is measured by means of the contour finder or in standard technics the dose is determined by using the measuring caliper Details of these instruments have been published [2, 3 4 6 7] and they are illustrated in Figures 22 7 8 9 10 11 12

treatment (with quantities of radium of the order of 10 Gm) finds its greatest usefulness in the treatment of cancers of the mouth and throat

The plan of treatment described below refers solely to patients with carcinoma of the mouth and throat

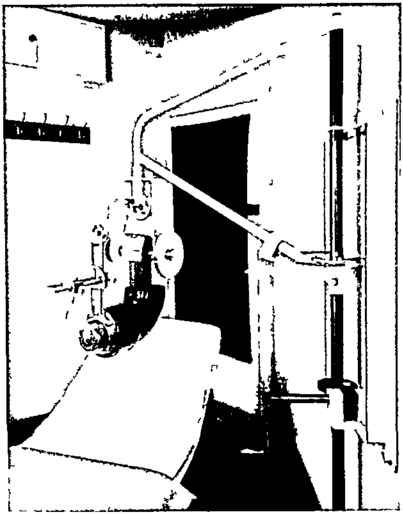


Fig 22 8 Wooden model of rad um beam unit used for measurements on pat ents

Type of Case Suitable for Treatment

The isodose curves of the 10 Gm radium beam unit (Figure 22 3) show that there is a very rapid fall in depth dose at 10 cm the depth dose is 15 per cent The radium beam treatment therefore is suitable for relatively superficial neoplasms only that is those at a depth of not more than 5 cm from the sur face It is for this reason that radium beam

General Plan of Treatment

The elimination of sepsis from the region to be irradiated is of great importance and time is saved by delaying radiation treatment until sepsis has been cleared

The treatment is planned to deliver a tumor icidal dose of radiation to the lymph nodes in the neck as well as to the primary growth

The first step in therapy is to decide ex

actly the region to be treated This is done by defining as far as possible the limits of the primary growth and its lymphatic spread In a patient with postcricoid carcinoma soft tissue roentgenograms are helpful in defining the lower limit of the primary growth The particular arrangement of fields is then marked out on the patient s skin planning wherever possible that the primary tumor is treated through regions bearing lymph nodes whether or not palpable lymph nodes are present The arrangement of fields is then investigated physically using either the measuring caliper or the contour finder Any modifications in the planned arrangement of fields or direction of the beam found to be necessary in the light of the isodose distribution obtained are then made

A dose of approximately 6 000 r is delivered to the tumor and regional nodes over a period of forty two days The tumor dose therefore is given at the rate of 1 000 r per week Both longer and shorter periods of treatment have been tried but this has been found the most satisfactory Patients receive one or sometimes two treatments per day The duration of each treatment is 22 5 minutes and the dose delivered on the skin in this time is 400 r The aim of 6 000 r tumor dose in forty two days is necessarily varied according to the condition of the patient and the reactions obtained

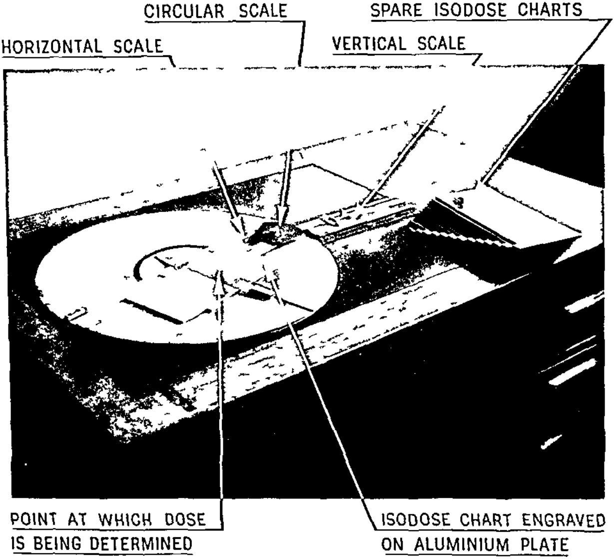


Fig 22 9 Calculating table used in the estimation of dosage from caliper measurements

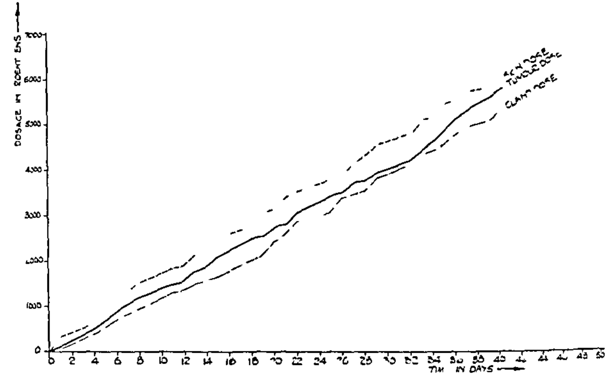


Fig 22 10 Dosage graph showing rising total in roentgens to tumor lymph nodes and skin during treatment

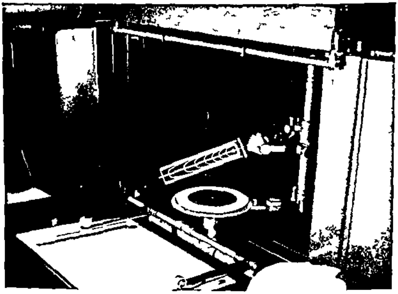


Fig 22 11 General v ew of contour f nder

In most cases it has been found possible to deliver the total dose of radiation to both primary tumor and regional nodes by radium beam There have been some cases however in which it was undesirable to give any further irradiation to the region bearing lymph nodes but in which some induration was still left at the site of the primary growth In such cases further treatment is given to the primary growth by other means (radium applicator needling or by diathermy excision) The timing of the accessory treatment is important

Fig 22 12 Completed dose contours mounted in plaster cast of patient The tumor represented by black area was on lateral border of tongue

and should be carried out as soon as possible after the radium beam treatment is completed to prevent any involvement of lymph nodes from viable cancer cells at the primary site

Certain standard arrangements of fields have become adopted for particular sites In intrinsic carcinoma of the larynx cervical metastases are late and rare and therefore treatment is given to the primary growth only In cases where lymph nodes are palpable in a region not covered by the standard arrangement of fields special fields are provided to treat such metastases In Figures 22 13 to 22 16 the standard arrangement of fields and the direction of the beam through each field found suitable for treating various sites are shown Beneath this is seen the isodose contours determined by the contour finder for such an arrangement of fields in a typical patient

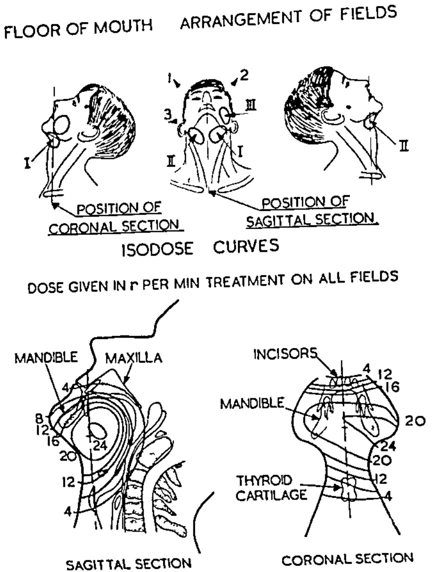
Typical reactions of the mucous membranes and skin are recorded in graphic form in Figure 22 17, this graph also shows the rate of regression of tumor and metastases in regional nodes in a case responding favorably to the dosage shown in Figure 22 10

The constitutional effect of the radiation is rarely a limiting factor Weekly blood counts taken throughout treatment on a series of 250 patients showed a leukopenia due almost entirely to a diminution in lymphocytes Very rarely did the leukopenia interfere with treatment Patients usually attend daily treatment as outpatients only those in poor general condition being hospitalized

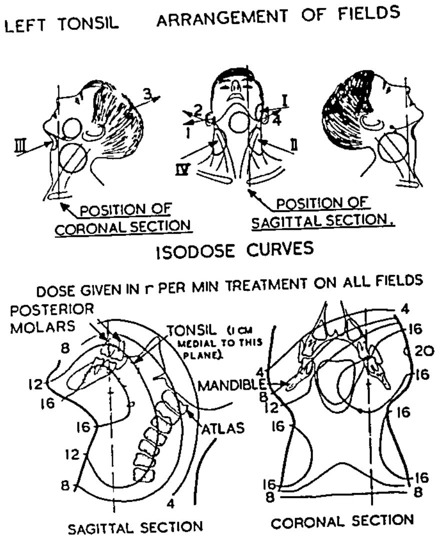
End Results

The figures of Tables 22 1 to 22 4 represent an unselected group of cases of all degrees of advancement Palliation was the most that could be hoped for in many cases no patient being refused treatment on account of the advanced stage of the disease

In each table the first column shows the period under consideration and the second column (a) the number of patients alive at the beginning of this period The third and fourth columns (b and c) show the number of patients passing out of observation during the period for the reasons given at the heads of these columns A patient who died of intercurrent disease halfway through the period might have developed a recurrence of cancer in the second half of the period had he lived He was exposed to the risk of dying from cancer for only half the period In calculating the cancer mortality for that period the average number of patients exposed to the risk of death from cancer (d) is therefore the total number entering the period minus half the total of Columns b and c The sixth column shows the number of cancer deaths recorded (e) and the cancer mortality is then $100\times\frac{e}{d}$ Thus in Table 22 2 the cancer mortality in the first year is 26 per cent The percentage surviving the first year therefore is 74 per cent the mortality in the



F g 22 13 Standard a ra g m nts of f elds of t eatment w th asso iat d do e ontours for ca rs of the floor of the mouth



F g 22 14 Standa d arrangement of f elds of t atme t with associated dose conto rs for ca cers of the tons l

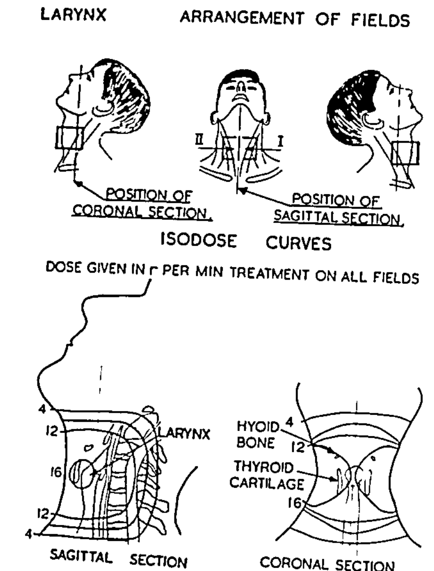


Fig 22.15 Standard arrangement of fields of treatment with associated dose contours for cancers of the larynx

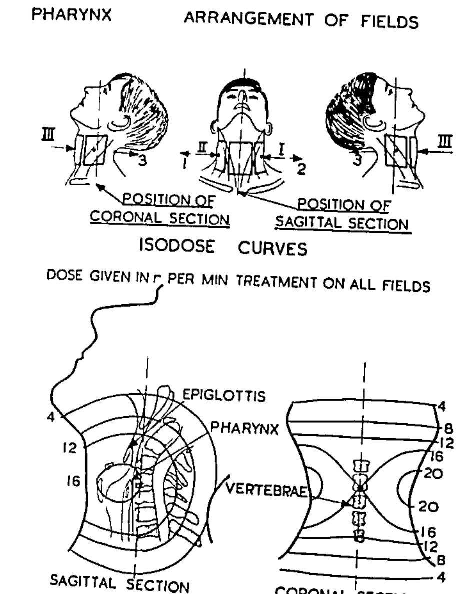


Fig 22.16 Standard arrangement of fields of treatment with associated dose contours for cancers of the pharynx

second year is also 26 per cent so the percentage surviving the second year is 74 per cent of 74 per cent, i e , 54 per cent

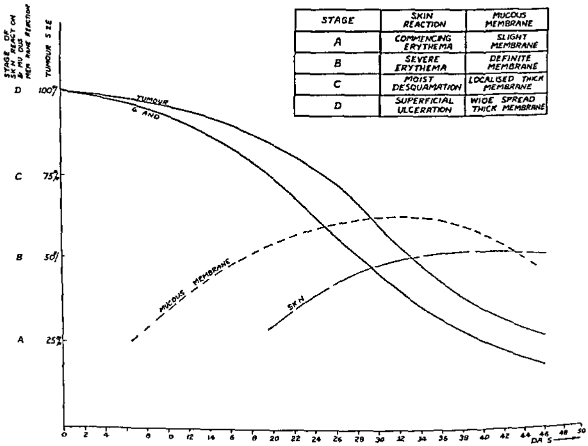
CARCINOMA OF FLOOR OF THE MOUTH

Table 22 1 presents the end results of 49 patients with carcinoma of the floor of the mouth Sixty seven per cent had lymph nodes palpable at the beginning of the treatment The five year survival figure is 33 per cent

CARCINOMA OF THE PHARYNX

In Table 22-4 177 cases of carcinoma of the pharynx are analyzed Of these patients 71 per cent had lymph nodes palpable at th beginning of treatment The growth in many cases was too advanced for the site of origin to be ascertained The average five year survival rate for this very advanced group of cases is 14 per cent

From studies made on the regression time of the tumor and the lymphatic metastases it



STAGE	SKIN REACTION	MUCOUS MEMBRANE
A	COMMENCING ERYTHEMA	SLIGHT MEMBRANE
B	SEVERE ERYTHEMA	DEFINITE MEMBRANE
C	MOIST DESQUAMATION	LOCALISED THICK MEMBRANE
D	SUPERFICIAL ULCERATION	WIDE SPREAD THICK MEMBRANE

Fig 22 17 Reaction graph

CARCINOMA OF THE TONSIL

In Table 22 2 76 cases of carcinoma of the tonsil are analyzed—71 per cent had lymph nodes palpable at the beginning of treatment The five year survival figure is 37 per cent

CARCINOMA OF THE LARYNX

In Table 22 3 48 cases of intrinsic carcinoma of the larynx involving one or both true cords are analyzed The five year survival rate is 35 per cent

was found that there were about as many cases in which the metastases in lymph nodes responded more rapidly than the tumor as there were cases in which the tumor responded more rapidly than the metastases It is concluded that when comparable doses are given to each the metastases in cervical nodes offer no greater resistance to radiation treatment than does the primary growth

An experimental comparison between gamma rays and x rays in the treatment of cancer of the mouth and throat was carried

TABLE 22 1 —RESULTS OF RADIUM BEAM THERAPY FOR CANCER OF THE FLOOR OF THE MOUTH

Period from treatment years	Patients entering the period	Patients passing out of observation during the period: Intercurrent deaths	Patients passing out of observation during the period: Living patients	Average number of patients under observation	Number of cancer deaths	Cancer mortality per cent	Survivors in each period per cent	Survival rate per cent
	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*
0–1	49	5	0	46 5	20	43	57	57
1–2	24	2	0	23	5	22	78	45
2–3	17	0	0	17	3	18	82	37
3–4	14	1	2	12 5	0	0	100	37
4–5	11	1	1	10	1	10	90	33

All stages of cancer Total number of patients seen 51 Total number of patients treated 4[illegible]

TABLE 22 2 —RESULTS OF RADIUM BEAM THERAPY FOR CANCER OF THE TONSIL

Period from treatment years	Patients entering the period	Patients passing out of observation during the period: Intercurrent deaths	Patients passing out of observation during the period: Living patients	Average number of patients under observation	Number of cancer deaths	Cancer mortality per cent	Survivors in each period per cent	Survival rate per cent
	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*
0–1	76	7	0	72 5	19	26	74	74
1–2	50	1	0	49 5	13	26	74	54
2–3	36	2	0	35	8	23	77	42
3–4	26	0	2	25	3	12	88	37
4–5	21	0	1	20 5	0	0	100	37

All stages of cancer Total number of patients seen 79 Total number of patients treated 7[illegible]

TABLE 22 3 —RESULTS OF RADIUM BEAM THERAPY FOR CANCER OF THE LARYNX

Period from treatment years	Patients entering the period	Patients passing out of observation during the period: Intercurrent deaths	Patients passing out of observation during the period: Living patients	Average number of patients under observation	Number of cancer deaths	Cancer mortality per cent	Survivors in each period per cent	Survival rate per cent
	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*
0–1	48	3	0	46 5	22	47	53	53
1–2	23	1	0	22 5	5	22	78	41
2–3	17	2	1	15 5	1	6	94	38
3–4	13	0	0	13	0	0	100	38
4–5	13	0	4	11	1	9	91	35

All stages of cancer Total number of patients seen 50 Total number of patients treated 48

TABLE 22 4 —RESULTS OF RADIUM BEAM THERAPY FOR CANCER OF THE PHARYNX

Period from treatment years	Patients entering the period	Patients passing out of observation during the period		Average number of patients under observation	Number of cancer deaths	Cancer mortality per cent	Survivors in each period per cent	Survival rate per cent
		Intercurrent deaths	Living patients					
	a	b	c	d	e	f	g	h
0–1	177	6	0	174	95	55	45	45
1–2	76	5	0	73 5	31	42	58	26
2–3	40	2	0	39	9	23	77	20
3–4	29	2	1	27 5	6	22	78	16
4–5	20	0	3	18 5	2	11	89	14

All stages of cancer Total number of patients seen 188 Total number of patients treated 177

out at the Radiotherapeutic Research Unit from 1942 to 1945 The radiation beam from a 200 kv x ray set was so modified that the isodose curves matched as closely as possible those of the 10 Gm radium beam A parallel series of patients was then treated with the x ray and radium beam using the same technic of treatment In this way the effect of wavelength alone could be determined No significant differences were observed in the patients immediate responses to the two types of wavelength except in the reaction of the skin which was more severe in those patients treated with x rays It was found that the ratio of gamma ray dose to x ray dose for the same severity of skin reaction was 1 34 There was no significant difference between the survival rates of the two series of patients It is concluded therefore that the wavelength of the radiation per se within the limits of the experiment i e 200 kv and 2 mev has no significant effect on the clinical results

ASSESSMENT OF RADIUM BEAM THERAPY

At the time when the radium beam unit was designed x ray therapy sets generally available operated at 200 kv No apparatus capable of producing 2 million volt x rays had yet been developed The quality or penetrating power of the gamma rays of radium is equivalent approximately to that of x rays generated at 2 million volts During the past decade rapid advances have been made in the design and construction of supervoltage x ray apparatus that can produce x rays at 2 million volts and over If the conclusions of the previous paragraph are accepted namely that the wavelength or energy of radiation per se between 200 kv and 2 mev has no significant effect on the clinical results then the great advantage to be expected from the use of supervoltage x rays is the enormously improved dose distribution within the patient that can be obtained by this means This improved depth dose greatly facilitates the treatment of deeply situated tumors The depth dose obtainable from a 10 Gm radium beam unit Figure 22 3 is lower than that obtained with a 200 kv x ray set owing to the short radium skin distance (8 3 cm) necessary to obtain a high enough intensity for therapy With a 2 mev x ray apparatus a satisfactory intensity for therapy can be obtained at a focal skin distance of the order of 1 meter The depth dose obtained with such apparatus is therefore little affected by the inverse square law and is very much better than that obtained by any existing radium beam units

During the past few years the development of nuclear reactors has made possible the production of artificially produced radioactive substances that can be used as substitutes for the naturally occurring radium These substitutes can be obtained much more cheaply than radium and in much larger quantities The most important of these substances at the present time is radioactive cobalt Quantities of the order of 2 000 curies of cobalt are now being produced and used as the radioactive source in telecurie units Such units are just

the same in principle as the radium beam or teleradium unit already described A source of 2 000 curies of cobalt however emits gamma rays of an intensity equivalent to more than 2 000 Gm of radium The cost of such a cobalt source is of the order of $30 000 The use of any equivalent quantity of radium is not practical since the cost of the radium is more than one thousand times as great as that of the cobalt A telecurie unit with a source of 2 000 curies of cobalt can be used at a focal skin distance of 75 to 100 cm thus giving a depth dose similar to that of a 2 mev x ray machine The disadvantage of the small depth dose of the radium beam unit no longer holds in the case of the telecurie unit which can therefore be used for treating more deeply situated tumors (Chap 28)

A radium beam unit of the type described above is convenient to work giving almost trouble free service over a long time It may be regarded as the forerunner of the modern telecurie unit It is effective in the treatment of cancer in relatively superficial sites such as the mouth and throat and existing apparatus of this kind can therefore still fulfill a useful function

CHAPTER 23

Multiple Source Radium Beam Therapy

Douglas Quick
and
Jeanne Delano Richmond

The radium beam unit to be described was designed by and constructed under the immediate supervision of Dr. Gioacchino Failla. It contains 50 Gm. of radium in the form of radium sulfate divided into 25 2 Gm. capsules that are distributed, equally spaced, in a stainless steel ring 30 cm. in diameter. The radium capsules themselves are of monel with an outer jacket of steel to protect against mercury. When the radium is in a treating position, each capsule coincides precisely with a conical collimating channel through the lead shielding at the bottom of the beam head. The capsules and collimating channels are angled inwardly approximately 23° from the vertical so that the 25 individual beams come together at a focus 35 cm. perpendicularly below the plane of the radium ring, the distance from a single capsule to the focus being 38.1 cm.

There are several advantages to this arrangement. If the radium were to be used as a single source, either the source would be very thick with a small cross section in order to simulate a point source, or the radium would have to be spread out over a comparatively large area. With a thick source, a large part of the radiation would be absorbed by the high filtration of the intervening radium itself. With a large flat source, the sizable penumbra would be objectionable. With 25 individual sources, collimation of the radiation is accomplished more easily, and since the separate beams do not overlap completely until they reach a distance of 35 cm. below the plane of the radium, the radiation dose to any point on the skin is much less than that at the focus. The 35-cm. distance between sources and focus was determined assuming a 25 cm. source skin distance to be reasonable for an ideal tumor depth of 10 cm. The diameter of the combined beams at this depth is about 7 cm. A longer source focus distance would reduce the output at the tumor while giving a greater relative depth dose. A shorter distance would reduce the amount of space between head and skin or reduce the lead for protection and collimation.

In the treating position, the radium-carrying ring is at the bottom of a steel cylinder surrounded by lead. A one-sixteenth inch steel plate forms the bottom of the steel cylinder and the radiation enters the collimating channels through this. In order to cut off radiation when setting up patients, etc., the ring is raised through a pool of mercury approximately 14 cm. deep, which then acts as a shutter beneath the radium (from Position 5 to Position 11 in Figure 23.1). Additional protection is afforded by the lead at the bottom of the container, since the capsules are not in direct alignment with their individual channels. The amount of radiation escaping directly beneath the beam head is then less than 6 mr/hr. The motion of the radium carrying ring is controlled from outside the room, with an interlocking electric switch on the door such that entering the room automatically causes the radium to rise into its protected or safe position. The walls of the beam head are of lead and steel approximately 21 cm. thick, affording this protection between the nearest

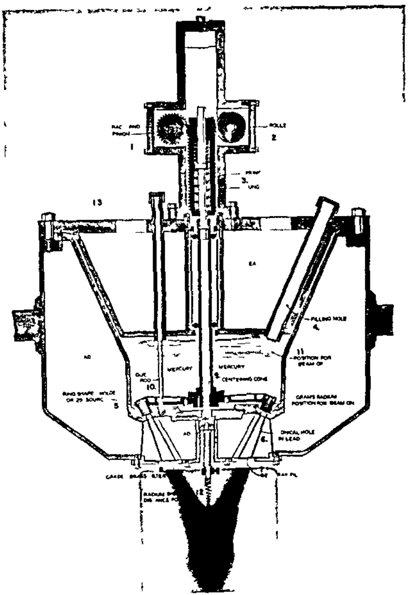


Fig 23 1 Diagram of a cross section of the radium beam head 1 Rack and pinion for controlling motion of radium-carrying ring 2 Guiding roller 3 Spring compressed to force out mercury at bottom of cylinder when radium is in treating position 4 Filling hole through which radium was inserted in Belgium 5 Treating position of radium-carrying ring showing position and angulation of radium capsule 6 Conical collimating channel through lead 7 Brass beta ray filter covering bottom of beam head 8 Removable graded brass filter covering bottom of high point of radiation 9 Cone for centering radium-carrying ring 10 Guide rod to prevent rotation of ring 11 Off or safe position of ring at top of mercury pool 12 Central pointer along which radium skin distance is measured 13 Location of machinery on top of beam head concealed by cover

Lead encased in stainless steel surrounds the unit and the assemblage of the beam head by bolts in the upper corners of the diagramed beam head can be seen As actually viewed in the treatment room the cylinder is extended upward by a cover that conceals the gearing and motor placed on the top of the beam head so that only the very top of the plunger housing shows

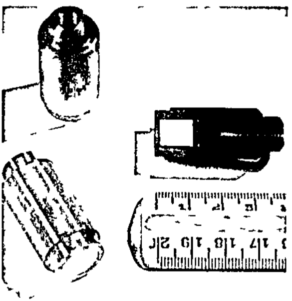


Fig 23 2 Radium sulfate salt is contained in monel tube with an outer steel jacket

radium capsule and any point outside the container while mercury and additional lead are between more distant capsules

The movement of the radium carrying ring is controlled by a rack and pinion driven by a motor through a worm gear (shown as 1 in Figure 23 1) Rollers guide the motion and a heavy spring is compressed by the motor after the ring reaches the bottom thus forcing out any mercury that might remain between a capsule and the steel and absorb some of the radiation (2 and 3 in Figure 23 1) The radium is raised by reversing the motor Limit switches automatically stop the motor at the on or off positions after the respective spring has been compressed by a predetermined amount There is also a manual control wheel by which the ring could be raised in the event of a power failure To insure that each capsule is accurately centered over its correspondin

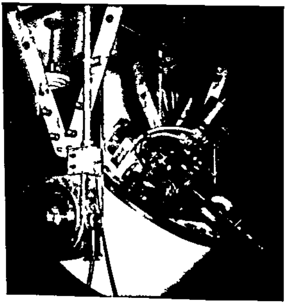


Fig 23-3 Motor-driven mechanism for lowering radium through mercury from safe position to treating position and for angulating beam head

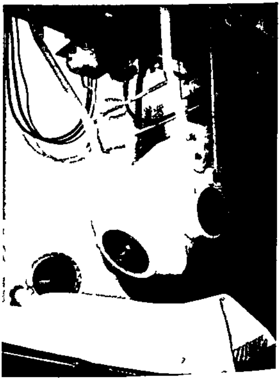


Fig 23-4 Radium beam unit is supported on I beam track under ceiling Unit is mechanized and can be moved across room on track Beam head is angled and patient is in place on table ready for final positioning

channel the ring as it comes down fits over a tapered pin in the center which keeps it centrally adjusted (9) Also the ring is prevented from turning by a rod parallel to its axis and line of motion (10) The entire assembly for raising and lowering the ring can be removed in case of needed repairs without any necessity for disturbing the radium

In order to place the radium capsules in the ring the top portion of the unit was sent to Belgium attached to a rough lead bottom shield There each capsule was individually

inserted into position through the filling hole in the top of the container (4), the ring then being rotated to the position of the next capsule Meanwhile the permanent bottom of the beam head was installed in the beam room here suspended from rollers on a ceil ing track and filled with mercury Then it was necessary only to hoist the top and radium carrying portions of the beam head out of the shipping container by means of rigger s equipment brought down through a trap door in the ceiling of the treatment room move the permanent bottom of the beam head under the top part by controls from outside the room and lower the top

The beam room itself has walls of concrete two feet thick and is entered through a half inch lead lined door and a maze An observa tion window consists of a truncated cone of water two feet thick through which patients can be seen from outside during their treat ments The beam head is mercury tight and can be rotated completely around however it is generally used at any angle between its vertical and horizontal positions only since this provides all the angulation necessary Al though the container can be moved across the room in practice it has been left in one place in good view of the observation window and the hydraulic treatment table moved The treatment table can be raised or lowered electrically and also tilted thus facilitating the setting up of patients The angle of tilt of the table is determined by a level and pro tractor arrangement attached to the side of the table This angle as well as the angle of the beam head from the vertical and the dis tance from the bottom of the beam head to the skin of the patient necessary to put the focal plane at the tumor level (measured along the center pointer 12) can be pre scribed for each individual patient and re produced at each successive treatment

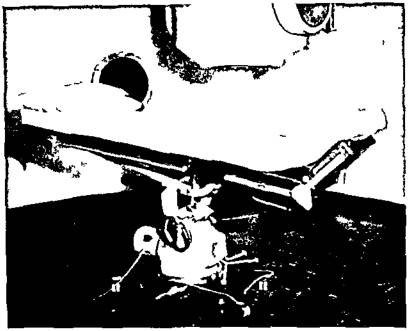


Fig 23 5 Hydraul c table on which patients are treated can be raised or lowered and angled to facil tate position ng of patients Protractor and level dev ce for determination of table angulation not shown

The twenty five sources cannot give more radiation at the focus than would a single source and this output is reduced by some self absorption of the salt and the absorptions of the monel and steel in the capsule the steel plate holding the mercury a brass beta ray filter on the outside of the bottom of the beam head (7) and the amount of tissue intervening between the beam head and the focus which amount depends on the particu lar setup for a patient When the focus is 10 cm below the skin the output is 3 r per minute There is however a central higher

point of radiation about 7 5 cm above the focus where the inner edges of the 25 beams begin to cross since the distance from the sources to this point is less than that from sources to focus Thus the isodose curves obtained with the radium unit are very different from those obtained with other sources of radiation being somewhat similar to those recently encountered in horizontal or short

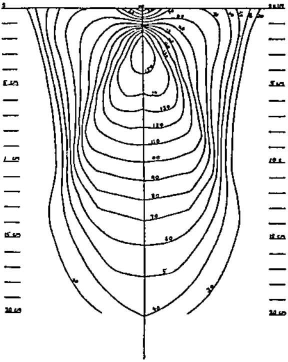


Fig 23-6 Isodose curve without graded brass filter Dose is in percentage of dose at focus mid line 10 cm deep Beam head–skin distance is 11 7 cm

axis rotation therapy The effect of the high point has been considerably lessened by a graded brass filter (8) which fits on the bottom of the beam head and extends halfway out over the brass beta ray filter covering the 25 beam apertures thus reducing the radiation in the inner half of the ring without appreciably lowering the dose at the focus

Turning from the strictly engineering features of this special type of beam head some of the clinical advantages are apparent and others have been revealed by experience

It was believed that 50 Gm of radium was the minimum quantity that would afford a full working range and an experience of five years has proved this to be correct The radiation source is a fixed and nonfluctuating quantity and is so far the best proved quality of therapeutic radiation The patient capacity is limited numerically With a standard type of patient setup the tumor dose at 10 cm depth is 3 r per minute we believe this slow dosage delivery is advantageous

The multiple converging beam arrangement permits delivering a lethal tumor dose or a destructive normal tissue dose without gross

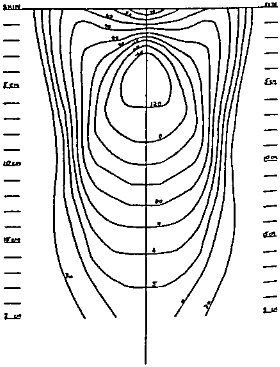


Fig 23 7 Isodose curve with graded brass filter Dose is in percentage of dose at focus mid line 10 cm deep Beam head–skin distance is 11 7 cm

surface tissue damage (Skin reactions are no longer limiting factors) Five years of experience with this equipment are not enough to warrant a detailed discussion of relative dosages but data are steadily being collected on tolerance of various tissues to large doses of gamma radiation from radium doses that vary in intensity and also in over all total delivery time Relative tolerances reveal interesting data such as the resistance of bone to this quality of radiation as compared with conventional high voltage X radiation

A few clinical comments will explain our impression regarding this modality Five years use does not permit a critical evaluation Results in widely divergent cancer groups not previously experienced have been obtained

These range through the more advanced head and neck cancers lung and bladder cancers certain of the more resistant kidney tumors female pelvic cancer and a suggestion of encouragement in some of the primary bone tumors

A quality of irradiation that is much less damaging to normal tissues and permits a better and more favorable co operative effort between irradiation and operative surgery becomes a reasonable practical possibility

An ideal arrangement would consist of several units of this basic type but with the multiple beam patterns varied to suit each one of several rather standard anatomic distribution problems commonly met with in radiation therapy practice Our circular beam with a focal plane of 3 inch diameter is admirably suited to many of the head and neck problems to localized but otherwise inoperable lung cancer to urinary bladder tumors to the external irradiation phase of uterine cancer therapy, and to many other problems of limited spread of the disease A long oval or rectangular field pattern would be more suitable for full mediastinal irradiation in esophageal carcinoma or any extensive mediastinal node involvement problem Total pelvic irradiation would be best handled by a rectangular field of a size different from the one just referred to and another variation would best handle the majority of breast problems especially with the renewed interest in MacWhirter s plan for the care of breast cancer At the other extreme a beam with focal plane of very small diameter—for instance half the size of our present beam—would be extremely valuable under some circumstances

From our experience to date we are convinced that the basic principle involved in this particular unit is capable of adaptation in various ways and to substantial advantage for the better handling of many of our more difficult and more resistant therapy problems

Clinical Application of Radioactive Isotopes

Editorial Introduction

Artificial Radioisotopes in the Treatment of Cancer

In the decade that artificial isotopes have been available from the chain reacting pile they have found extensive use Their applications in the field of medicine have been mainly in the realm of research especially in the studies of intermediary metabolism New applications in diagnostic procedures are continually being found The use of I^{131} in the study of thyroid disorders of radioactive iodinated serum albumin to localize brain tumors of radioactive chromated red cells to study red cell volume and the use of radioactive phosphorus to localize tumors of the eye represent but a few of the diagnostic uses for radioisotopes Ingenious experiments are being performed in efforts to localize the radioactive isotopes within tumors Although physical measurements often indicate a rather high specific activity of concentration of the radioactive isotopes by the tumor in excess of that of the surrounding tissue the differential is not great enough in most instances to effect a marked destruction of the cancer without producing excessive damage to normal structures An exception however is seen in certain forms of thyroid cancer where the avidity of the neoplasm for the radioactive isotope is so great as to bind quantities of radioactive iodine lethal to the tumor The ablation of the thyroid gland partially enhances the avidity of metastatic thyroid cancer to concentrate the radioiodine Methods may be developed to block other metabolic pathways in which administered radioactive isotopes may participate so that they may be shunted into the metabolism of a given neoplasm and thereby aid in the destruction of the neoplasm Although many experiments are being performed at present with this in sight the editors have not felt justified to include them in these volumes Throughout these volumes an effort has been made to present the methods now being successfully used in the treatment of cancer by radioactive isotopes

The utilization of artificial radioisotopes for human therapy has opened an entirely new vista of radiology Artificial isotopes although often used as a substitute for the naturally occurring ones such as radium are used also in clinical situations where radium and its decay products cannot be used

The newer methods of administering irradiation introduce problems of dosimetry that have not been worked out to the satisfaction of all to date The earliest efforts to express dosimetry of artificial radioisotopes were those in which efforts were made to correlate a given dose with an equivalent dose of X or gamma radiation The unit of exposure of x ray is the roentgen defined as that quantity of X or gamma radiation such that the associated corpuscular emission per 0 001293 G of air (1 cc at STP) produces in air ions carrying one electrostatic unit of electricity of either sign

Inasmuch as the roentgen is a true expression of dose only when it applies for air and only when it applies to X or gamma rays efforts have been made to express radiation dosages in tissues based on the quantitation of energy absorption in tissue At the Sixth International Congress of Radiology in 1950 the erg per gram was adopted as the official basic unit in which all radiation dosages including X and gamma ray doses should be measured One unit for measuring isotopes that has been used fairly extensively has been the REP (roentgen equivalent physical) this is defined as that amount of ionizing radiation producing 93 erg/g of energy absorption in tissue This value was selected to be the same as energy absorbed by water exposed to hard x rays The REP has not been officially accepted There is no especial reason why the energy of the REP and the

roentgen should be equal At the Seventh International Congress of Radiology in 1953 the unit accepted for expressing dosage of radio isotopes was the RAD which is defined as the dose producing energy absorption in any irradiated material equal to 100 ergs per gram

RADs are particularly suited to beta particle dosimetry For a tracer application in medicine the maximum quantity of radioisotope administered is limited by that amount which will give a radiation dose no greater than 0 3 RAD per week

Physicists are now busily engaged in developing a uniform method of expressing the quantity and type of radiation for a given isotope Efforts to correlate the dose of radiation from an isotope with that of a given known source have been made A frequent such use is the correlation of millicuries of cobalt in terms of milligrams of radium This attempted correlation can be misleading It would be better to express the gamma equivalence of the two isotopes and possibly express the output in r per hour A unit the rhm the r per hour at one meter was devised for this purpose The future will offer a satisfactory expression of dosage of radiation from radioisotopes in biologic systems as more is learned about the distribution of the isotope within the organism a correlation between expressions of physical dose and biologic effects will be obtained

The following list includes the radioisotopes now commercially available for treating cancer *

1 Sterile colloidal radiogold This is a stable colloid of Au^{198} containing approximately 4 to 5 mc/mg of Au^{198} and having an activity of 15 to 90 mc/cc Other specific activities for special uses are available

2 Sterile silver on radiogold colloid This is a modification of the above in which high specific activity gold has on it a coating of silver or silver oxide changing somewhat its biologic behavior

3 Sterile chromic radiophosphate This is a *suspension in dextrose* of ignited and finely ground chromic phosphate having a particle size of 0 2 to 0 4 μ Somewhat experimental it is being used as a pure β emitter for intracavitary and interstitial irradiations

* After Tabern

4 *Cobalt needles* Stainless steel needles containing cobalt wire and giving activities per centimeter of length approximately equivalent to radium

5 Cobalt alloy sources This highly resistant alloy, either alone or enclosed in glass or metal units, provides a source of monochromatic radiation for the cells ovoids etc of Ernst, Fletcher Hymen and other applicators The cost is only a fraction of that of the corresponding amount of radium

6 Cobalt in nylon This same alloy enclosed in flexible nylon catheter tubing provides a unique source of radiation for regions where 'fixed forms are not applicable

7 Strontium β ray applicators These are designed to provide a convenient source of 1 2 mev β rays for external use and eye irradiations in particular

8 Sodium radioiodide solutions These provide diluted sodium radioiodide solutions for therapeutic doses For the uptake studies that usually precede therapy more dilute solutions and capsules are available

9 Sterile sodium radiophosphate This likewise provides a solution containing approximately 1 mc/cc of P^{32} for oral or intravenous administration of that isotope for the treatment of polycythemia vera and chronic myelogenous leukemia

10 Among the therapeutic preparations still in the developmental state are Y^{90} a pure β emitter forming complexes with body proteins and with proper amounts of carrier remaining well localized in tissues Auroseeds similar in physical form to the familiar radon seeds have as active agent the pure γ emission of Au^{198} and may be cut at the point of use to give seeds of any desired activity

Table Ed Introd 1 presents a resume of the different methods of administering artificial radioactive isotopes and the cancers for which they are used The last column lists the location within these volumes where a description of the use of a given isotope is provided The editors have attempted to present a *bird s-eye* view of the present accomplishments in the field of treating cancer with radioactive isotopes The entire subject is in a state of dynamic flux and many changes are anticipated in the near future

TABLE Ed Introd 1—THE APPLICATION OF ARTIFICIAL RADIOISOTOPES IN CANCER THERAPY

Method of administration	*Isotope*	*For treatment of*	*Presented in*
Parenteral administration	P^{32}	Leukemia	Vol I Chap 25 Vol IX Chap 12
		Polycythemia vera	Vol IX Chap 17
	I^{131}	Thyroid cancer	Vol III Chap 47
	Au^{198} $CrP^{32}O_4$	Leukemia	Vol I Chap 24
	Boron Subjected to neutron beam in vivo	Brain tumors	Vol II Chap [illegible]
Surface application	P^{32}	Superficial skin lesions	Vol I Chap 24
	Sr^{90}	Ophthalmologic lesions	
	Au^{198}	Mold therapy of skin cancer	Vol I Chap 24
Interstitial injection	Au^{198}	Carcinoma of prostate	Vol VII Chap 7
		Carcinoma of cervix	Vol I Chap 24
	$CrP^{32}O$	Same as Au^{198}	Vol I Chap 24
Interstitial implantation	Co^{60}	All instances where interstitial radium needles and seeds have been used	Vol I Chap 27
	Au^{198}	As replacement for gold radon seeds	Vol I Chap 26
	I^{131}	Carcinoma of pancreas	Vol V Chap 21
	Au^{198} Coated by silver	Bronchogenic carcinoma	Vol I Chap 24
	Ta	Bladder tumors	Vol I Chap 24
Intracavitary infiltration	Au^{198} $CrP^{32}O$ Y^{90}	Ascites and hydro thorax due to cancer	Vol I Chap 24
		Postoperatively to prevent seeding of cancer	
Intracavitary implantation	Co^{60}	Bladder tumors	Vol I Chap 27
	Au^{198}	Uterine cancer	Vol VI Chap 5
	Na^{24} Br^{82}	Have been used for bladder tumors	
External therapy (teletherapy)	Co^{60}	Most localized cancers	Vol I Chap 28

CHAPTER 24

General Principles in the Therapeutic Use of Artificial Radioactive Isotopes

Paul F Hahn

INTRODUCTION

During the fifty five years in which roentgen rays have been used in the treatment of cancer and a somewhat shorter period during which radium and radon have been used for similar purposes a wealth of information concerning ionizing radiations and their effect on neoplastic and normal tissue has accumulated Earlier empirical methods of application of their ionizing radiations have now been reduced to more systematic and scientific methods The introduction of the cyclotron in the early 1930 s followed shortly by the discovery of artificial radioactivity and ten years later by the development of the chain reacting pile have all contributed immensely to the potential future of radiation therapy Many problems have arisen and been solved with regard to purification measurement handling and disposal of these useful agents At present there are approximately 1 000 artificial radioactive isotopes that have been described many of which by virtue of their physical characteristics are available for biologic and medical uses

The various criteria for acceptability of these isotopes in human therapy have been discussed elsewhere [9] Such criteria are necessarily arbitrary since changing conditions the discovery of new isotopes by various reactions the development of more efficient separation procedures development of new reactors with higher neutron flux and finally a better appreciation of the biologic handling of many of the rare elements have all contributed to make practical the use of a wider variety of isotopes Many nuclides because of their exceedingly short half lives may seldom or never see any practical application in therapy Even here an exception is to be noted as for example in the in vivo induction of radioactivity in boron by thermal neutrons in the treatment of brain tumors [5] Excessively long half lives militate against the in vivo use of certain nuclides in human therapy In spite of the limitations several dozen nuclides have found useful application in therapy and the radiotherapist is presented with many other new sources of radiation with a wide variety of spectra many of which may be almost tailor made to his needs

ARTIFICIAL RADIOISOTOPES AS SUBSTITUTES FOR X RAYS AND RADIUM

Many look upon artificial radioactive isotopes solely as substitutes for earlier existing radiation measures This is not necessarily so It is true that Co^{60} teletherapy represents a satisfactory substitute for supervoltage x ray in the one million volt range with advantages in economy both in initial installation and upkeep In those instances where the 250 kv dose range is more suitable the interstitial use of isotopes can sometime offer certain advantages Limitation of dosage by skin erythema is eliminated Furthermore the inverse square law operates in favor of the therapist rather than against him It is of interest that if radium were to have been discovered during the past 15 years along with most of the other radioactive isotopes, it would very likely never have been used in cancer therapy [12] There is available a wide variety of nuclides that have

more suitable characteristics than radium Radium is an exceedingly toxic carcinogenic agent when ingested which must be encapsulated in platinum needles or tubes the breakage of which can become a very serious problem In the past 8 years cobalt needles have been used extensively in clinical interstitial implantation therapy Cobalt like radium is also filtered with platinum in order to screen out the greater part of the beta particle emanation since both materials are used primarily millicurie dosage desired the end being pinched for closure during this process The gold wire seeds do not require the careful handling during sterilization and implantation that is necessary to avoid rupture of the radon seeds [17] From a standpoint of dosimetry there are disadvantages at the present time in the use of the gold seeds inasmuch as little empirical information is available and the usually used radon dose tables cannot be used because of the large discrepancy in the gamma

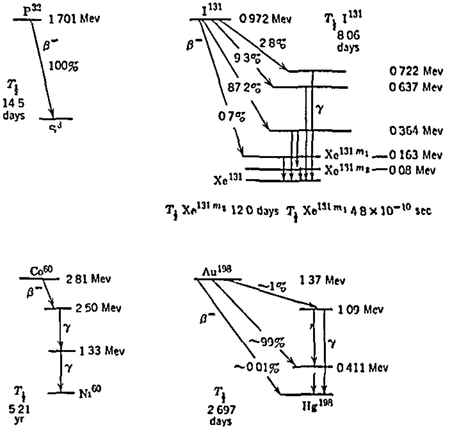


Fig 24 1 Decay schemes

in a cross-fire of gamma irradiation to minimize local necrosis Ta^{182} and Ir^{192} are currently under study for use in similar forms of therapy Cs^{137} a fission product has a desirable half life of 37 years and a gamma energy of 0 7 mev but like radium has the disadvantage of difficulty of encapsulation and danger in case of breakage [17 29]

The use of Au^{198} seeds as a substitute for radon is becoming more and more popular [31 38] Here radioactive gold wire is introduced into a piece of nonradioactive gold tubing and the seeds are cut off according to the energies and in the additional difference in half lives From a standpoint of safety the gold has two definite advantages the first being that no radioactive gas can escape from these seeds and the second that protection in handling is much easier because the half value in lead for gold is approximately one third that of radon For example a lead container for storage of nylon ribbon loaded with Au^{198} seeds weighs approximately 50 pounds In contrast to the storage of equivalent amounts (millicuries) of radium which would weigh 400 pounds From a viewpoint of cost figures

are not readily available or comparable at the present time Considerable differences would result, depending upon whether or not the hospital had its own radon plant

The recently introduced means of im plantation of radon seeds small radium cap sules cobalt sources and gold seeds in nylon ribbon have found fairly wide acceptability owing to decreased exposure to operating per sonnel during implantation [18] Together with radon seeds the Au^{198} seeds have the advan tage that they do not have to be recovered from the ribbons The further advantage in the gold is again its low half value in lead

ARTIFICIAL RADIOISOTOPES AS A DISTINCT METHOD OF RADIATION THERAPY

Systemic Administration

The other artificial radioactive isotopes that have been most concerned in therapy of can cer are P^{3} , I^{131} and Au^{198} in the form of radioactive colloidal sol

RADIOACTIVE PHOSPHORUS

P^{3} was first used in therapy twenty years ago in the treatment of leukemia During the next few years this use was extended to the treatment of polycythemia vera Its popularity in the treatment of leukemia has diminished somewhat recently owing probably to the development and popularity of a wide variety of chemotherapeutic agents Osgood has con tributed a great deal to the maintenance ther apy approach in the use of P^{3} Many in vestigators object to the use of this nuclide because of the lack of specificity of phos phorus for the bone marrow, its salts tending to go to most cells in the body The use of this agent in the control of polycythemia vera has increased steadily There are differences of opinion as to whether this disease should be considered the erythrocytic analogue of leu kemia and therefore a malignant disease It now seems fairly generally agreed that there is some real increase in the terminal incidence of fulminating leukemia in P^{3} treatment of polycythemia vera The writer accordingly be lieves that phlebotomy deserves a trial in most cases of polycythemia and that in the difficult cases where problems of microcytosis etc develop and are otherwise troublesome to handle by bleeding this is time enough in which to introduce P^{1} therapy Owing to the relatively long half life of P^{3} the time for dissipation of the radioactivity is fairly con siderable requiring about 2 months to deliver 97 per cent of the total energy The long life span of the erythrocyte must be recognized These factors make it difficult to titrate the patient response Thus, the individual with an abnormally high erythrocyte count if treated with P^{32} alone is subject to possible complica tions such as thrombotic accidents during the first month or two under therapy unless vene section is resorted to at the time isotope treat ment is initiated Much of the popularity of P^{3} therapy in polycythemia vera has possibly stemmed from the notion that has become more and more widespread that a pure beta emitting isotope is safe to handle Liberaliza tion of allocations for use of this isotope have probably been based largely upon such a con ception

RADIOACTIVE IODINE

Early uses of I^{130} were confined largely to the treatment of thyrotoxicosis and it was not until shortly after 1940 that serious attempts were made to use this isotope and I^{131} in the treatment of thyroid cancer

The accumulation of radioiodine by meta static carcinoma of the thyroid gland was re ported by Keston Ball Frantz and Palmer in 1942 [21] Seidlin Marinelli and Oshry in 1943 [35] used I^{131} in the treatment of meta static adenocarcinoma of the thyroid At first the attempts were somewhat discouraging in asmuch as only about 15 per cent of the cases showed uptake of iodine nuclides by the meta static tumors However it was subsequently found that ablation of the thyroid either sur gically or by irradiation with the iodine iso tope was frequently followed by an increased uptake by the distant lesions Also by ad ministration of thyroid stimulating hormone and the judicious use of thiouricil, ultimately a larger number of patients became reasonable candidates for therapy

It must be kept in mind that the incidence of thyroid cancer is fairly low This tumor appearing in only about 1 per cent of all the cancer population does not represent the serious problem with which we are faced in

comparison with tumors of the breast ovary cervix prostate stomach and lung A great deal of the early emphasis of artificial isotope therapy in carcinoma of the thyroid can be ascribed to the ready availability of these nuclides even in prereactor days At the present time I^{131} is obtained as a fission product and is therefore available in almost unlimited quantities In some circles there is currently a resurgence of interest in I^{130} but this is largely concerned with use of the material in the treatment of thyrotoxicosis and is again based upon the added ability to titrate the radiation response

According to Pochin [33] several general points are now widely accepted in the conduct of treatment of carcinoma of the thyroid with I^{131} (1) Any thyroid carcinoma that can be wholly removed at operation should be treated surgically rather than by radioiodine (2) Many tumors that ultimately concentrate iodine do not do so until after ablation of the thyroid gland by surgery or radioactive iodine (3) Highly differentiated carcinomas with colloid filled follicles are more likely to concentrate and retain radioiodine than anaplastic tumors (4) Anaplastic tumors are better treated by radiotherapy with or without surgery than by radioiodine

It must be kept in mind however that some cases of relatively differentiated tumors with good iodine uptake show little response to treatment On the other hand in cases of anaplastic tumors a good response may occur although the uptake of iodine has been poor or even impossible to detect by external counting methods In general however the effects of treatment appear to run parallel to the degree of uptake

Pochin has described the selection of patients for thyroid ablation When the latter procedure is indicated he has stated the pros and cons for surgical removal and for radioiodine destruction of the gland (1) Surgical removal avoids unnecessary exposure to radiation of the patient whose survival may depend on how much subsequent radioiodine can be administered without inducing hypoplasia or aplasia of the bone marrow (2) Valuable time may be gained since radiation therapy with radioiodine can be begun promptly after operation avoiding waiting until the side effects of an ablation dose have disappeared (3) It can be combined with resection of as much tumor tissue as can safely be removed

On the other hand when structures of the neck have been altered by previous operation such that there is a risk of damage to the recurrent laryngeal nerves or parathyroids thyroidectomy may be dangerous Radioiodine ablation is indicated if one recurrent nerve is already destroyed or if several previous thyroid operations have been performed or if the thyroid is densely infiltrated and adherent The dose should be sufficient to insure actual destruction of the gland without being so large as to cause excessive total radiation

As to dosage for ablations the amounts used in Great Britain are in general higher than in this country The widely used dosage here would be from 25 to 35 mc whereas the British use a dose of 75 to 80 mc for this purpose In using higher ablation doses much concern has been expressed concerning the radiation that may be directed to the hepatic tissue With an 80 mc dose it has been estimated [33] that the liver radiation might exceed 1 000 RADs In our rather extensive experience in which selective irradiation to the liver is accomplished by the intravenous administration of radioactive colloids we have found however that 2 500 RADs or more are well tolerated by the human and have shown that in the dog it is necessary to administer as much as 60 000 to 80 000 RADs before irreversible pathologic changes result [13] It seems likely then that the limiting factor in dosage would more likely be the bone marrow rather than the hepatic tissue tolerance to side effects of thyroid irradiation The thyroid gland may become moderately tender during the period in which the gland radioiodine is being rapidly discharged according to Howes and Foot Similarly cervical lymph nodes may become tender and decreased in size during the week following the ablation dose even though little radioiodine uptake apparently occurs Following an ablation dose edema may develop in the thyroid or in nearby functioning metastases causing embarrassment to breathing and therefore intubation and tracheotomy procedures must be considered as a possible emergency part of such treatment

Usually the radioiodine treatment of the tumor is useless until tracer evidence indicates concentration of the nuclide Such concentration may be evident before thyroid ablation or it may require some weeks following such procedure If uptake is poor, thiouricil or its derivatives is given [33 34] for two or more months at a dosage of 0 6 to 1 5 Gm per day After discontinuance of the drug for 2 days another uptake study should be made if concentration in the metastases is shown to be favorable a therapeutic dose is then given immediately

Many points arise as to decisions concerning the advisability of administering therapeutic doses immediately following ablation maintenance of the myxedematous state or attempts to increase the uptake by the administration of thyroid stimulating hormone or a series of thiouricil treatments The many individual variations in the size and location of the metastatic tumor tissue the *extent of uptake* in various locations all require a considerable amount of judiciousness in making decisions as to continued treatment and the extent thereof since it must always be kept in mind that the limitation of this form of therapy lies in the ability of the body to withstand general radiation and in particular of the bone marrow to do so

Dosages for the therapeutic use of iodine following ablation range from 100 to 150 mc orally at intervals of 3 to 4 months As in the use of radiocolloids by vein for treatment of leukemia (see below), where there is concentration of the material in the RE system *hematologic changes are the rule* immediately following isotope administration In practically all cases however these changes often limitated to the lymphocytic elements are transitory Occasionally however rather persistent leukopenia anemia and thrombocytopenia occur which of course require cessation of therapy

Reduction in the size of the tumor or meta*static lesions does not necessarily* indicate uptake of the radioiodine There are a number of cases in this type of therapy as well as in

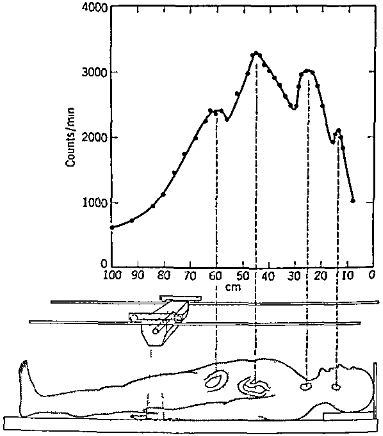


Fig 24 2 Profile distribution after thyroid ablation

radiogold treatment of Hodgkin s disease and leukemia in which there is no evidence of localization of the material and still lymph glands decrease markedly in size suggesting in the over all that there is a humoral effect ascribable to the irradiation In the use of radioiodine many of these alterations in size of the lesions are preceded by tenderness

Instrumental monitoring of the patient is of course highly advisable and much more feasible over the past few years during which time a number of variations of scintiscanners have been on the market Improvements in such instruments are being made constantly and semiquantitation of uptake by various lesions is becoming more and more feasible A discussion of the radiation hazards in connection with the use of iodine can be found by consulting other sources that take up such problems in detail [33]

There is a considerably greater hazard in handling patients treated with massive doses of iodine than in the instances of other isotopes, since the excretion problems become highly important (saliva sweat urine etc) It must be remembered that the tolerance of the euthyroid patients toward radiation is relatively small and that small fractions of the therapeutic doses employed in carcinoma of the thyroid could be highly dangerous As to distribution of patients it is preferred in some centers to treat patients in special wards where the staff is familiar with the problems involved

RADIOACTIVE GOLD

Radiogold colloids were first introduced by Hahn and Sheppard in 1946 as therapeutic agents against cancer At the time they were at first looked upon as a pile substitute for previously used I^{130} colloid and $Mn^5 O_2$ colloids for intravenous treatment of diseases involving the reticulo endothelial system The latter nuclides being made by cyclotrons were entirely too expensive and otherwise unsuited for large scale clinical use On the other hand metallic gold colloids seemed highly suitable with regard to practically all characteristics including economy of production in the reactor and other criteria for such therapeutic radioactive agents [9 11] In the beginning they were used primarily by the intravenous route in the treatment of acute and chronic leukemias and in Hodgkin s disease In acute leukemias in children one survival of 12 months and one of 9 months were recorded in 12 cases treated but otherwise in general the results were not too encouraging In the treatment of chronic myelogenous and lymphogenous leukemia however excellent remissions of from 4 to 6 months duration have been uniformly obtained following the intravenous administration of approximately 50 mc of the colloid [9 13] Among the advantages of using this material are (1) It may be administered to ambulant patients in a single intravenous dose making unnecessary the hospitalization or repeated return of patients as is required for X irradiation to the spleen (2) There is a negligible degree of radiation sickness encountered and that in only a small percentage of the patients treated owing presumably to the integration of the radiation of dose deliverance (3) The metallic colloid is nontoxic and does not give rise to immunologic or dermatologic reaction (4) Metallic gold being insoluble in body fluids usually remains at the site of original deposition the latter depending upon the route of administration (5) There is no problem of radioactive excreta (6) The biologic and physical half lives being the same owing to lack of excretion simplifies the measurement of dosage received (7) The gamma radiation from this isotope is of low enough intensity that only small amounts of lead shielding are necessary for personnel protection (8) Because of the gamma component of the spectrum calibration of the material is facilitated and losses due to spillage can be quantitated on sponges etc by means of conventional quartz fiber electrometers (9) External body measurements are made possible because of this gamma component (10) There is a considerable latitude in the tolerance to dosage given by most routes employed

Seventy eight patients with chronic myelogenous and lymphogenous leukemia have been treated Among the earlier cases inasmuch as there was no experience upon which to base the dosage many of the individuals were undoubtedly grossly undertreated in an attempt to be conservative In spite of this there were several remissions obtained with doses of as little as 10 mc of gold In general however it

has been found that 50 to 60 mc by vein are uniformly followed by good response to treatment In one instance inadvertently a dose of 100 mc was administered which was followed by a remission of 2 5 years This would suggest that perhaps further studies at such higher dosage levels should be made [9 15]

In a collaborative investigation between our laboratory and that of the Radioisotope Unit of the Nashville Veterans Administration Hospital alternate use of gold and x ray therapy has been carried out in a series of 16 patients [15] Clinical and hematologic responses were similar in all instances However, in the case of gold therapy the incidence of radiation sickness was negligible and patients who had two or three remissions by each form of therapy invariably expressed a preference for the single administration of the gold isotope method Complications encountered were similar in both instances e g , the development of hemorrhagic diathesis, gradually increasing lack of reduction of the spleen as the number of treatments increased and finally the relatively high incidence of terminal fulminating leukemia which is nonresponsive to therapy

Our group has treated 35 patients with Hodgkin s disease by the intravenous administration of radioactive colloids over the last 10 year period most of them at the beginning of this therapeutic study There was no choice of patients as to whether it was a granuloma paragranuloma or sarcoma In 7 patients there were dramatic responses However introduction of nitrogen mustard as a means of treatment of this disease was at that time greeted so enthusiastically it was not felt justifiable to deprive the patient of what might be a better form of therapy It is now believed that gold *in combination* with chemotherapeutics which are currently being used in the treatment of leukemias and Hodgkin s disease should be studied [9]

Intracavitary Instillation

RADIOACTIVE GOLD

About 80 per cent of the radioactive gold currently being produced at Oak Ridge (20 curies per week) is being employed in the palliation of advanced tumors in which abdominal ascites and pleural effusion are the chief concern In 1945 Muller reported the successful suppression of abdominal ascites following the administration of a short lived Zn^{63} isotope [30] In 1947 we demonstrated the localization of radioactive gold colloids in the peritoneal cavity following intraperitoneal injection of this material [14] Since 1949 Muller and many others have reported on the use of such gold colloids for suppression of fluid formation in both the pleural and peritoneal cavities The general consensus of all these reports would seem to be that from 50 to 80 per cent of patients treated have benefited definitely

The mechanism of the reaction is poorly understood The normally ultramicroscopic colloidal gold particles following injection into the peritoneal cavity become condensed within 1 to 2 days into visible dotlike particles in the cytoplasm of the macrophages These cells loaded with gold particles maintain their structural and functional integrity and are probably mobilized toward the mesothelial surface of the serosa [8] In any case a fairly uniform deposition on the serosal surface is obtained and frequency of tapping is usually markedly decreased and sometimes made unnecessary for periods of 4 to 6 months or longer The commonly employed intraperitoneal dose is from 125 to 150 mc and the intrapleural dose to one side is from 50 to 125 mc An approximation of the beta dose to the surface of the peritoneum has been calculated by Chamberlain assuming a surface of 30 000 sq cm as equal to 3 000 RADs per 100 mc of gold injected Owing to the low half path (0 4 mm) about 90 per cent of the ionization resulting from the beta particles occurs within the first mm of exposed serosa Thus this reaction is a superficial one this would explain the lack of undesirable secondary radiation effects on the mucosa of the intestine and other viscera The amount of gold that obtains access to the circulation and thus ultimately to the liver is very small and can be ignored As cited earlier the tolerance of the liver to irradiation is very considerable and is not remotely approached by use of gold by this route

RADIOACTIVE CHROMIC PHOSPHATE

A number of investigators have studied the use of radioactive chromic phosphate as first developed by Jones Wrobel and Lyons as a

substitute for gold in the palliative therapy of fluid formation Such preparations are not truly colloidal in nature but are rather a suspension of particles that tend to agglomerate upon contact with the peritoneal fluid and have a tendency to puddle in the lower peritoneal cavity There is also a significant degree of dissociation of the labile phosphorus which behaves like inorganic phosphate going into many tissues and excreted by the urine Clinical studies are promising expected to be a bone seeker Its clinical effectiveness has not been established

USE OF RADIOISOTOPES FOR TREATING BLADDER TUMORS

Treatment of bladder tumors with radioisotopes has been actively investigated since 1948 Harris and Freedman used solid sources placed at the center of rubber bags However it was found that a relatively slight displacement of such a source under operating con

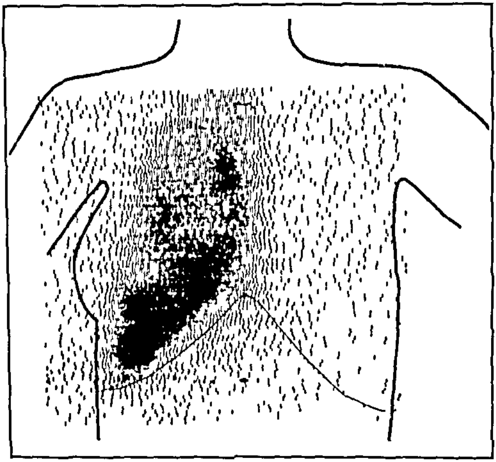


Fig 24 3 Pattern of radioactivity as shown by scintiscanner

but have not been adequately evaluated for this material as yet The long half life and lack of a gamma ray rendering the isotope safe for clinical use are attractions for its use

RADIOACTIVE YTTRIUM

Another isotope being considered for intracavitary use is Y Although administered as a chloride it is said to behave like a colloid This might explain why it is claimed to stay localized in the region of the cavity of injection inasmuch as it would normally be

ditions could increase the dose from one side of the bladder to as much as three times that received in the other This does not occur when solutions are used It has been demonstrated that gross distortion of the shape of the balloon does not effect distribution of the dose to the surface as shown by studies of Smithers Wallace Trott Sinclair Mayneord and Walton in England who used solutions of Na and Br for such purposes They preferred a large sized balloon to insure a closer fit to the bladder wall At the same time

Muller was developing a similar method using radioactive cobalt in a small bag Recently Ellis and Oliver showed that the bag could be dispensed with by using colloidal gold introduced directly into the bladder At the same time methods were being developed for the interstitial implantation of radioactive sources such as Ta^{1} wire and Au^{198} grains encased in platinum For treatment with the bag technic or by direct instillation of radioactive fluids one must not expect more than so later the isotope is instilled A bottle draining the urine is monitored so that an immediate indication may be given should the bag burst The active solution is also colored to enable immediate detection by eye as well as by counter The patient is properly sedated before the bladder is dilated In short term irradiation, about 800 mc of Br is used and in longer term irradiations about 250 mc A total volume of about 150 ml is used to distend the balloon Under such conditions about

Fig 24-4 Position of bag in Br^{8} treatment of carcinoma of the urinary bladder

10 per cent of the total number of bladder tumors to be suitable for therapy Those most suitable are the ones with generalized tumor involvement of the bladder mucosa where there are multiple tumors or several tumors with large areas of intervening abnormal mucosa and in which there is no clinical radiologic or histologic evidence of spread of the neoplasm into the bladder muscle Using the bag technic Smithers Wallace, and Trott proceed roughly as follows The bag is inserted per urethram in the female patient and through perineal incision in the male The patient is returned to the ward and a day or 0 3 mc per ml will deliver a dose of the order of 2 000 RADs at the surface of the balloon in about 2 days

In the work of Ellis and Oliver without a rubber bag using colloidal radioactive gold it was found that precipitation of the gold in the bladder wall did not occur in the longest period 2 5 hours used in their investigation (Figure 24 4) Here the bladder was first drained and then using a protected syringe 300 mc of the Au^{198} colloid were injected and retained in the bladder by means of a Foley catheter

Smithers *et al* have described in detail the

use of Ta^{18} wire which could be successfully threaded through certain types of bladder tumors and subsequently upon completion of the irradiation be withdrawn through the urethra thus not necessitating a second operation Thus no implant material remains permanently in the bladder as is the case in the use of radon or gold seeds both of which cause thickening of the bladder wall

BETA RAY APPLICATORS

Beta ray applicators have found use primarily in the field of dermatology and ophthalmology Earlier types using radium were unsatisfactory because the concomitant gamma radiation made protection difficult Low Beer first used radioactive phosphorus by soaking blotting paper in a solution of sodium phosphate³ and subsequently applying it to the tumor Such a flexible source lends itself to application to contours of the body in such conditions as basal cell carcinoma hyperkeratoses and hemangiomas Friedell and his collaborators prepared applicators containing Sr^{90} in equilibrium with Y^{90} Sinclair developed polyethylene sheets containing 20 per cent red phosphorus subsequently irradiated in a pile for two weeks in flat sheets from which were obtained dose rates of the order of 1 000 to 2 000 r per hour The dosimetry of such applicators has been described [27] Modifications of beta applicators have been widely used at the Royal Cancer Hospital in England in the treatment of diseases of the cornea and epibulbar region Sr^{90} shells have been used more recently in place of the P^{3} buttons Lederman and Sinclair report on their uses in corneal ulceration stubborn forms of keratitis corneal vascularization limbal neoplasms and in spring catarrh

ARTIFICIAL RADIOISOTOPES FOR GAMMA IRRADIATION

Early in 1947 we first used radioactive colloidal gold interstitially in a patient with leukemia cutis whose lesions in the left parietal region of the head had not responded to intravenous administration of the isotope in spite of the fact that the hematologic picture was well controlled by the latter therapy Alternate lesions were infiltrated with fractional millicurie doses of colloid such as to deliver an estimated 7 000 to 12 000 beta equivalent roentgens to each Within 2 weeks the injected areas were flattened and deeply pigmented from the radiation [14] Subsequently gold colloids were used in the breast prostate cervix bladder and stomach tumors [9] as well as in exploratory research being done in localization for brain tumor therapy [28] In most of these instances the material is used in conjunction with surgery In the case of bladder tumors most of them do not call for irradiation of the entire mucosa and since the tumors usually consist of discrete masses sometimes only partially resectable we frequently have gold on hand on a standby basis during such operations Under such circumstances it is rather commonly undertaken to infiltrate the nonresectable portion of the tumor or the bed from which the tumor has been removed [36] Co^{60} and Ta^{18} applicators have been used extensively as substitutes for radium and radon for gamma applicators by Myers in the United States by Becker and Scheer in Germany and in the Royal Cancer Hospital (Figure 24 5)

CANCER OF THE PROSTATE

Our efforts to treat carcinoma of the prostate by the transurethral or rectal approach in some thirty patients were not attended by any considerable degree of success The difficulty apparently lies in the inability to distribute the colloid uniformly by these approaches [16] However Flocks Culp Elkins and Evans using the suprapubic route have employed the interstitial use of radioactive gold colloids in over four hundred cases By this approach it is possible to expose the prostate the lymphatics about the rectum the regional lymph nodes seminal vesicles and adjacent lymphatics so that either visualized or probable tumor can be thoroughly infiltrated with a radioactive material If it is resectable the tumor is removed and the adjacent area thoroughly infiltrated The layers of fascia about the prostate and seminal vesicles with their vessels and lymphatics form a fascial compartment aiding in holding the radioactive solution in the desired location Many tumors of the prostate are exceedingly dense and hard thus rendering advisable a syringe that can be used under considerable pressure

These investigators use a syringe that is also heavily shielded They administer approximately 1 5 mc of radioactive gold per Gm of involved tissue keeping the volume as low as possible usually under 12 ml in a prostate under 100 Gm in weight This might well mean that there would be 15 mc per cc concentration of the isotope If too large a volume is used they found that the fascial compartments were disrupted and the material spread beyond the desired area This produces possibility of rectal damage In our more recent use of gold in prostatic tumor therapy we have tended to go slightly higher to 2 mc administered per Gm of tissue and have had suprisingly little difficulty as regards complications

Flocks and co workers sometimes employ perineal injections under the following conditions (1) as a preliminary injection 3 weeks before retropubic exposure in order to fill uninvolved or slightly involved lymphatics with radioactive material (2) residual or recurrent nodules of carcinoma 2 months or more after retropubic injection (3) patients whose condition does not warrant suprapubic exposure or obese patients where suprapubic exposure would be difficult and probably inadequate, (4) aging patients with relatively small areas of carcinoma (5) in patients refusing total prostectomy or other types of operative administration of the material it has markedly reduced the number of complications of rectal ulceration requiring a colostomy and the formation of calculi The most important problem seems to be adequate distribution of the radioactive material throughout the neoplasm and along the fascial planes and lymphatics where spread has occurred The volume of material injected the site and method

Fig 24 5 Radiograph of tantalum wire implant for carcinoma of the urinary bladder

of injection the size of the tumor and the presence of involved lymph nodes are all of great importance Surgical removal of as much involved tissue as possible is absolutely essential This avoids late sloughing and calculus formation and permits the use of smaller doses and increased concentration of the dose in the remaining tissue

sian in St Louis and Kottmeier and Moberger in Stockholm have done considerable work in the use of gold colloids in cervical carcinoma The gold infiltration is directed toward the lateral pelvis A total volume of 35 ml is injected bilaterally into the parametria (Figure 24 7) Total dosage ranges from 120 to 150 mc depending upon the size of the

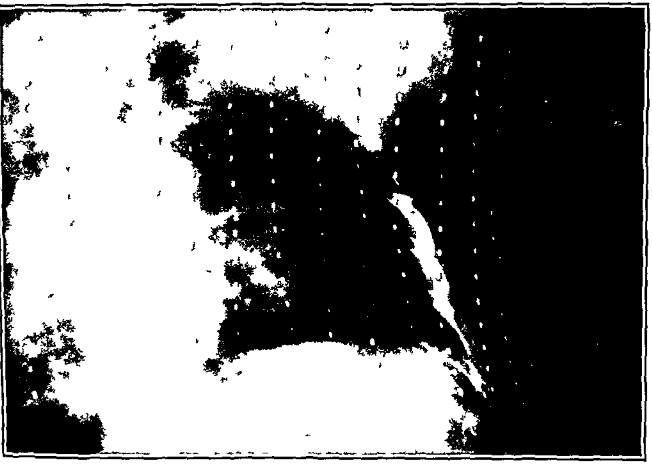


Fig 24-6 Planar nylon ribbon implant with Au^{198} seeds for large ulcerated carcinoma of the breast

CARCINOMA OF THE CERVIX AND VAGINA

In early 1947 we attempted to treat carcinoma of the cervix and the vagina by direct infiltration with radioactive colloidal gold [14] The results were not entirely satisfactory owing to the use of too small dosages In one instance the cauliflower like consistency of the tumor mass was such as not to retain the injected material It was pointed out that such tissues as well as those that are too highly vascular do not lend themselves to infiltration procedures with this isotope Allen Sherman Nolan Bonebreak and Ter Pogos

patient Gold therapy is accompanied by conventional intracavitary radium and in some instances is followed by Wertheim hysterectomy and lymphadenectomy Complications have been minimal there being occasionally a transient mild nausea for 1 or 2 days No changes in the blood picture have been noted that were of significance The chief complication encountered in their patients as well as in our own group has been pain Usually discomfort is noted in the pelvis upper thighs and buttocks starting with the *fourth or fifth* day postinjection This will usually have subsided by the second week Careful study of

the clinical results obtained tend to show a definite improvement over the results obtained with more conventional methods of therapy

BRONCHOGENIC CARCINOMA

A considerable amount of interest is attached to the problem of the bronchogenic tumor External radiation measures are accompanied by unfortunate sequelae such as pleural adhesions parenchymal damage and radiation necrosis of the bronchus trachea

Fig 24 7 Roentgenogram showing distribution of gold mixed with Diodrast immediately after the intraparametrial injection with superimposed areas of most commonly involved lymph nodes

etc when adequate amounts of radiation to eliminate the tumor are employed Pneumonectomy is the treatment of choice but this unfortunately largely because of the late diagnosis of this silent tumor has shown a 5 year cure rate of less than 5 per cent The major immediate problem involved is spread to the regional lymphatics chiefly the nodes of the mediastinum We have shown that when gold colloids are instilled into the bronchus they are slowly taken up by the lymph nodes but as much as two weeks are required for adequate drainage to afford radiation concentrations that would be satisfactorily high [10] Owing to the short half life of this isotope, the radiation has been dissipated in such a period of time thus obviating its use for such treatment We found that silver colloids were promptly drained. However their production by a transmutation reaction on palladium is inefficient and uneconomical, which would preclude their widespread use in therapy Therefore gold colloids coated with silver have been developed [10, 11] which physiologically and chemically behave like silver and have the physical characteristics of the gold nuclide Administered by the route mentioned they are frequently concentrated to several thousand times in the lymph nodes over and above residual concentrations in the lobe of the lung originally treated Thus it becomes possible to subject the mediastinal and other thoracic nodes to hundreds of thousands of equivalent roentgens resulting frequently in their complete obliteration It is recognized that nodes that are grossly involved with tumor tissue will probably not concentrate this material in the manner found in normal nodes but it is assumed that such grossly involved nodes will be removed at time of pneumonectomy Microscopic tumor emboli however might

well be expected to be adequately irradiated and thus we feel that this approach offers a hopeful adjunct procedure to surgery in the treatment of this commonly encountered tumor More recently we have shown that following pneumonectomy when such silver coated gold colloids are directly injected into the empty hemithorax there is also a satisfactory concentration of the radioactive material in the thoracic lymph nodes [10 26] Thus at the present time it is suggested that 2 weeks preceding operation instillation into an intact lobe of the lung on the affected side be undertaken Two weeks later in order to allow for proper uptake and irradiation of the lymphatics and to furnish protection to the operator pneumonectomy is performed Shortly following the operative procedure the empty chest is injected to provide further irradiation to the lymphatics At the present writing we have only such patients who have survived for 2 5 years or less which is too early to evaluate the effectiveness of this procedure

CHAPTER 25

The Clinical Application of Systemic Radioactive Isotopes in Cancer Therapy

William F Bethard
and
Leon O Jacobson

The criteria for using radioisotopes by systemic administration depends upon the physical chemical and biologic characteristics of the nuclide

Initially the toxicity of the element itself must be determined If high specific activities are available this may not be crucial but as in the case of radiogallium the total number of atoms required may approach the number toxic to the organism Secondly chronic exposure of undiseased tissues to ionizing radiations is considered undesirable and for this reason radioactive isotopes having relatively short physical half lives have been preferable Such half lives however must be of sufficient length to permit adequate production and processing periods Recently more emphasis has been given to the time in which radio active atoms remain within tissues rather than the duration of radioactivity per se Biologically the former is more important and its consideration permits the use of otherwise remotely feasible isotopes C^{14} having a physical half life of 5 600 years was not administered to human beings for a long time on the premise that its retention would result in prolonged exposure to radiation Tracer doses used with caution upon fatally ill individuals revealed that approximately 60 per cent of the radioactivity was eliminated within 5 days and that the excretory rate continued to be rapid thereafter Such data have provided a basis for bolder and immeasurably valuable human tracer experiments The time during which tissues are exposed to radiation from internally administered radioisotopes is referred to as the effective half life and this is dependent upon both the rate of excretion and the rate of physical decay For purposes of tissue dose estimation the effective half life of any isotope that is excreted in an exponential manner may be approximated by the following relationship

$$\text{Effective half life} = \frac{\text{Physical half life} \times \text{biologic half life}}{\text{Physical half life} + \text{biologic half life}}$$

where the biologic half life is determined by the rate of excretion from the organism In some cases e g I^{131} it is simpler and more accurate to determine the effective half life directly In this case periodic measurements of radiation over the thyroid gland are made in a consistent manner From these values plotted semilogarithmically as a function of time the half time may be ascertained In su cases knowing the effective and physical ha lives the rate of excretion may be calculate

As the last criterion in the choice of a isotope therapeutic utility depends to a great degree upon its affinity for the tissue needin treatment All forms of ionizing radiation probably result ultimately in identical biologic effects hence the only advantage of internally administered sources is the ability to minimize radiation received by normal cells With these criteria to be considered the prodigious number of known radioactive isotopes is automatically abridged so that a minimum number of appropriate ones remain Most of those applicable to therapy can also be used

for tracer studies but the reverse is not true. Individually adequate tracers may be unsuitable therapeutically. Radioisotopes considered in detail here will be mostly confined to those whose therapeutic usefulness has been carefully evaluated.

RADIOACTIVE PHOSPHORUS

Natural phosphorus is composed of but a single isotope P^{31}. Of three common radioactive isotopes, only P^{32} is sufficiently long lived to be useful biologically.

P^{32} was first introduced into the treatment of leukemia by Lawrence, Scott and Tuttle in 1939. Known radiosensitivity of these tumors suggested that "chemoradiation" would be of value. Theoretically, phosphorus is utilized proportionately to rate of tissue growth. Thus the more rapidly growing malignant cells accumulate more P^{32} than normal cells and receive a majority of the radiation. This is based upon the apparently valid assumption that the artificial isotope possesses chemical properties identical to the natural element. Tissue analyses by tracer technics indicate a tendency toward preferential concentration of phosphorus in cells of the reticulo endothelial system. The capacity of tumors to take up phosphorus is variable and corresponds roughly to the efficacy of P^{32} therapy in the type of tumor encountered.

P^{32} can be obtained by neutron bombardment of stable sulfur, stable chlorine or natural phosphorus. The last is rarely used because of the relatively low specific activity of the final preparation. Oak Ridge Laboratories provide the carrier free isotope (i.e. every atom radioactive) produced by exposure of sulfur to the interior of an uranium pile. It is usually supplied as di hydrogen sodium phosphate in a hypotonic solution of about pH 2.0. Both the pH and the tonicity are best adjusted prior to intravenous use although such is unnecessary for the oral route. Chemical neutrality as indicated by phenol red may be obtained by dropwise addition of 10 per cent sodium hydroxide and tonicity may be altered toward physiologic by dilution with normal saline. Occasionally distilled water may contain sufficient calcium and magnesium as impurities to cause precipitation of the phosphorus. According to the National Bureau of Standards, this may be prevented by the use of 0.001 molar phosphoric acid (H_3PO_4) as diluent. In some tracer work, however, the presence of the carrier free salt is often desirable. The high specific activity available permits dilution as described above. A relative concentration of 2.0 mc. per ml. (1.0 mc. equals 37 million disintegrations per second) has proved to be optimum for most therapeutic occasions. After processing, sterilization by autoclave is indicated if intravenous use is contemplated. Although it is difficult to recover pathogenic bacteria from nonsterilized highly radioactive solutions, growth of certain fungi is supported.

Subcutaneous or intramuscular administration is contraindicated because of the extreme amount of irradiation received locally during absorption. Either oral or intravenous routes may be used. In the former, sterilization is unnecessary and the problem of handling "hot" syringes is avoided but relatively greater doses are required because of uncertain absorption. The latter may be reduced some by giving the solution when the stomach is empty and then withholding food for at least two hours. Foods containing much calcium or phosphorus should be particularly avoided on the day of administration. Within 6 days after ingestion of P^{32} by normal subjects 25 to 50 per cent is excreted in the urine and feces. In patients who have leukemia or polycythemia vera excretion is somewhat less (20 to 25 per cent of the total dose). Commonly the effective dose is considered to be 75 per cent of the total oral one. Intravenously, of course, absorption is 100 per cent but excretion may range from 5 to 25 per cent in patients with the aforementioned diseases. Nearly all such excretion is by the kidneys.

Radiophosphorus (P^{32}) emits monochromatic negative electrons and it has a physical half life of 14.3 days. The particles have a maximum energy of 1.69 mev which provides a maximum tissue range of 7 mm. In general, leukemias and lymphomas are best treated by frequent small doses while polycythemia vera responds best to a large initial dose. In the former 1 to 2.5 mc. per week are given until a remission is obtained or until bone marrow depression necessitates discontinuation. Pre

quent blood counts including platelets must be done and these must be interpreted in the light of the fact that P^{32} has a cumulative effect with a duration exceeding the specified one week interval. In polycythemia vera the initial dose is usually 4 to 6 mc, although this may be adjusted upward or downward according to the severity of the individual case. If remission is not obtained within three months the original dose or fraction thereof may be repeated. Individual variation is marked, hence some trial and error is unavoidable.

In other than freshly standardized solutions dose calculations must allow for radioactive decay. Since this is of exponential character, and since very little contamination is present, it is best done by plotting a decay curve (radioactivity as a function of time) on semilogarithmic paper so that the mid point corresponds to 50 per cent decay in 14.3 days. By this curve the original solution may be corrected when used on subsequent days.

Radiation dosage afforded by P^{32} can be calculated in equivalent roentgens according to the formula of Marinelli [17]. Except for academic interest, this is usually unnecessary, unless tracer work is being done in otherwise normal human beings. For simplification, it has been shown by Tobias that 1.1 μc of P^{32} distributed within a tissue volume of 1 kg body weight would, if all retained, deliver about 3 REP (roentgen equivalent physical) total body irradiation in the first day. The same dose would yield between 30 and 60 REP total irradiation if less than 50 per cent were excreted. Because of the affinity for reticulo endothelial tissues the majority of energy is expended there.

Perhaps the prime indication for the use of P^{32} at present is polycythemia vera. Prolonged and consistent remissions have been observed. Details of such use are given in another chapter. The response of chronic myelogenous leukemia to P^{32} is in general good but it is probably inferior to that obtained by Myleran. Reinhard *et al* reported results in 39 patients who were given frequent small doses. Nearly all had symptomatic as well as hematologic improvement but splenomegaly disappeared in only 10. It was the authors' impression that life was not greatly prolonged. Lawrence *et al* [16] have reviewed the results in 129 patients and have concluded that, although life was not significantly lengthened, morbidity was reduced. In general P^{32} compares favorably with x ray in the treatment of this disease.

"Neoplastic" diseases of the lymphatic system (i.e., lymphosarcoma, chronic lymphatic leukemia, and giant follicular lymphoma) respond to P^{32} less consistently than polycythemia vera and chronic myelogenous leukemia. Dose requirements are smaller and there is a greater tendency toward serious bone marrow depression. A few hematologists have considered abandoning P^{32} in these cases but in the authors' opinions a sufficiently great number of successes have been achieved to warrant continued trial. One must beware particularly of protracted severe thrombocytopenia. Often however lymphadenopathy and splenomegaly regress with minimal change in the level of formed elements in the peripheral circulation. X radiation undoubtedly remains the treatment of choice, but P^{32} may be substituted with some success.

Hodgkin's disease, multiple myeloma, malignant melanoma, Ewing's sarcoma, mycosis fungoides, and most carcinomas have all been subjected to P^{32} with notable lack of benefit. Carcinoma of the breast has been claimed to respond, but improvement is usually subjective and evanescent. All forms of acute leukemia are essentially unaffected. Reticulum cell sarcoma yields equivocal results.

There is no method by which an exactly appropriate dose of P^{32} can be predetermined. Response is individual and is not solely dependent upon calculations involving body weight, surface area, etc. Overdosage manifests itself by the usual signs of radiation damage, i.e., thrombocytopenia, leukopenia and later anemia. Bone marrow aplasia is seldom irreversible, however, providing the patient can be successfully supported.

RADIOACTIVE IODINE

Stable iodine consists of but a single isotope I^{127}, and although five radioactive isotopes are known, only two (I^{130} and I^{131}) possess physical characteristics suitable for biologic use. The lighter of these is not usually employed clinically because of its short physical half life of 12.6 hours. I^{131}, the one

utilized most in biology, can be produced by deuteron bombardment of tellurium in the cyclotron Since 1946 however the Atomic Energy Commission has made available car rier free radioiodine obtained from a nuclear reactor as a fission product of uranium Ship ments consist of sodium iodide (NaI) in a dilute solution of sodium hydrogen sulfite ($NaHSO_3$) having a pH of 11 Inasmuch as absorption from the gastrointestinal tract is uniform prompt and practically complete oral administration is favored by most users No processing of the original solution is required

I^{131} emits both beta and gamma radiations and has a physical half life of eight days The natural selectivity of the thyroid for iodine has allowed radioiodine to be used uniquely in both tracer experiments and therapeutics Conversely however it is not used in the general treatment of neoplastic disease Beta particles provide local tissue irradiation and gamma emanations permit external detection and quantitation at the sites of deposition

Experimental uses of radioiodine are suf ficiently specialized to be considered in detail elsewhere In summary it may be said that diagnostic tests of thyroid function have been devised and that they utilize the rate and quantity of radioiodine transit through the thyroid gland Some observers emphasize the percentage of administered dose found in the thyroid gland at a given time [22] Others emphasize the ratio of protein bound to free radioiodine in the plasma at unit time after administration [18] Which of these values corresponds most closely to the real clinical situation is conjecture In euthyroid states 10 to 45 per cent of the administered I^{131} will be fixed by the thyroid in 24 hours providing the test has not been preceded by iodine thyroid extract or antithyroid drug therapy The remainder of I^{131} is excreted in the urine within 3 days Similarly 10 to 45 per cent of the radioiodine appearing in the plasma in 24 hours will presumably be protein conjugated if thyroid function is normal In either test values higher than the ranges quoted suggest increased thyroid function and values lower decreased function

By virtue of the natural affinity of the thyroid for iodine and the beta emanations possessed by I^{131}, the latter is theoretically an ideal agent for treatment of hyperthyroidism The irreversible action of such therapy upon thyroid function and the ignorance of long term effects of irradiation, however compel discriminate use Pregnancy contraindicates use of I^{131}, particularly beyond the third month as then the fetal thyroid begins to accumulate iodine in ever increasing amounts Exposure of both mother and fetus to ionizing radiations should be kept minimal even before this time Until the riddle of chronic radiation damage is closer to solution other forms of treatment are perhaps wiser in the young hyperthyroid individual Except for these two generalizations choice of therapy is an in dividual matter dependent upon the judgment of the therapist Many believe that nodular toxic goiters should be removed surgically whereas diffuse toxic goiters may be treated in situ

In selection of suitable candidates for radio iodine therapy it is wise not only to have biopsy evidence of the sort of tumor to be treated but also to have additional indication that such a tumor can metabolize iodine The latter may be ascertained either by external gamma radiation measurements over the tu mor or by estimates of the percentage of administered iodine excreted in the urine Commonly both methods are employed Ex ternal survey of the body with a gamma sensitive device is of advantage in that hitherto unsuspected metastases may be detected

Treatment of thyroid carcinoma must not be limited to radioiodine It is extremely val uable but still an adjunct Well localized tu mors should be attacked in the most effective surgical manner, and one must not be lulled by the clinical indolence of the more highly differentiated types Radioactive iodine itself cannot be considered lightly Although rapid turnover allows large doses normal tissues occasionally display evidences of radiation injury Hemoglobin production, as measured by radioiron incorporation may be tempo rarily inhibited Hypoplasticity of all bone marrow elements may be seen upon biopsy Although infrequent fatal aplastic anemia has occurred The powerful adjunct must be used with caution and judgment

RADIOACTIVE SODIUM

Radioactive sodium (Na^{24}) has not been used extensively in treatment of neoplastic diseases because of its short physical half life (14 8 hours) and because of handling difficulties resulting from its energetic beta and gamma emanations Rather cumbersome protective measures are required Tracer amounts have been utilized for metabolic distribution and circulation studies but it is doubtful that these will ever become routine Therapeutic potentialities were first suggested by Hamilton and Stone in 1937 and these were expanded by Thygesen Videboeck and Villaume in 1944 Extensive clinical trials were reported by Evans *et al* in 1948 Radiosodium was administered orally as the chloride Absorption was prompt and complete distribution was general and excretion during the periods of observation was less than 10 per cent Results of treatment were considered to be satisfactory in chronic myelogenous leukemia chronic lymphatic leukemia and polycythemia vera Doses varied from 2 mc per week to 40 mc per month and they depended largely upon the individual response Inasmuch as selective uptake could not be demonstrated effective action was attributed to whole body irradiation It was concluded that Na^{1} yielded results comparable to but no better than other forms of radiation therapy

A second isotope Na is available for tracer studies but its long physical half life of 2 6 years prevents its use as a practical therapeutic agent

RADIOACTIVE GOLD

In searching for a radioactive isotope possessing suitable physical characteristics yet existing in colloidal form attention was directed toward gold Two such isotopes Au^{198} and Au^{199} existed Even though they were similar physically ease of production favored the former Au^{198} emits both beta particles and gamma rays and its physical half life is 2 7 days

Colloidal suspensions of Au^{198} have been administered intravenously in therapy of chronic leukemia [3] Improvement generally followed and remissions could be obtained but there was little evident advantage over more readily available agents Radiogold has also been used in treatment of serous effusions secondary to malignant tumors [2] Introduction of the isotope into the afflicted serous cavity frequently resulted in temporary cessation of fluid production hence comfort to the patient Dosage schedules and injection techniques have varied according to the judgment of individual therapists Generally amounts between 60 and 150 mc are employed Responses are inconsistent Past experience has indicated that best results are obtained in carcinoma of the ovary with peritoneal implants and ascites

Radiogold has also been utilized for direct injection into tumor tissue [11] By virtue of its colloidal properties gold is fixed in tissues at the site of injection so that very little enters the general circulation Neoplastic masses can thus be subjected to calculated amounts of irradiation by interstitial application Such therapy has been satisfactorily applied to carcinoma of the prostate [9] cervix [21] and breast It has the advantage of delivering a maximum amount of radiation to the tumor and a minimum amount to skin bowel and other adjacent normal tissues

RADIOACTIVE ARSENIC

Successful empirical use of arsenic in leukemia for nearly 100 years led to the idea that radioactive arsenic might be better Arsenic^{8} could be readily produced in a nuclear reactor by the Szilard Chalmers reaction in which a stable organic arsenic compound (cacodylic acid) is irradiated with final recovery of the desired isotope Physical half life is 26 8 hours and radiations include positrons beta particles and very energetic gamma rays General use is obviously impractical Metabolic studies [6] on various organisms including man have shown inconsistent species differences in excretion and tissue localization of arsenic For therapeutic purposes it may be considered that there is no selective uptake and that any effects are due to total body irradiation It has been estimated that 1 mc of As^{8} yields approximately one equivalent roentgen total body radiation Initially patients were given intravenously 0 5 to 2 0 mc As products of greater specific activity became available doses were increased to 65 and even 100 mc Because stable arsenic content was only 3 to 10 mg

TABLE 23-1 — PHYSICAL CHARACTERISTICS AND USES OF THE COMMON RADIOACTIVE ISOTOPES

Element	Usual isotopes	Physical half life	Type of radiation	Uses
Phosphorus	$_{15}P^{32}$	14.3 days	neg. beta	Therapy of polycythemia vera, chronic leukemias and lymphomas Intermediate carbohydrate, fat and protein metabolism Blood volume determination
Iodine	$_{53}I^{131}$	8.0 days	neg. beta gamma	Diagnosis and therapy of thyroid disorders Thyroid physiology Tagged protein metabolism Blood volume determinations Detection and localization of brain tumors
Sodium	$_{11}Na^{24}$	14.8 hours	neg. beta gamma	Therapy of chronic leukemias Electrolyte metabolism (adrenal and renal physiology) Sodium space measurement
	$_{11}Na^{22}$	2.6 years	positron gamma	Circulatory efficiency
Gold	$_{79}Au^{198}$	2.7 days	neg. beta gamma	Intravenous colloid therapy in reticuloendothelial neoplasms Local infiltration of tumors
Gallium	$_{31}Ga^{72}$	14.3 hours	neg. beta gamma	Therapy of bone tumor
Cobalt	$_{27}Co^{60}$	5.3 years	neg. beta gamma	Studies in hematopoiesis External gamma irradiation
Carbon	$_{6}C^{14}$	5,600 years	neg. beta	In vitro and in vivo experiments in biosynthesis and degradation
Sulfur	$_{16}S^{35}$	87.1 days	neg. beta	Amino acid metabolism Protein metabolism
Potassium	$_{19}K^{42}$	12.4 hours	neg. beta gamma	Electrolyte metabolism
	$_{19}K^{43}$	22.4 hours	neg. beta gamma	
Iron	$_{26}Fe^{55}$	3.0 years	neg. beta, gamma (very soft)	Studies in hematopoiesis, blood preservation, blood volumes and radiation damage
	$_{26}Fe^{59}$	47.0 days	neg. beta gamma	
Calcium	$_{20}Ca^{45}$	180.0 days	neg. beta	Mineral metabolism Bone growth
Strontium	$_{38}Sr^{85}$	65.0 days	gamma	
	$_{38}Sr^{89}$	53.0 days	neg. beta	Bone physiology Radiation effects in animals
Zinc	$_{38}Sr^{90}$	25.0 years	neg. beta	
	$_{30}Zn^{65}$	250 days	positrons gamma	Trace element kinetics White blood cell metabolism Carbonic anhydrase system
Manganese	$_{25}Mn^{52}$	6.5 days	positron gamma	Enzyme chemistry
	$_{25}Mn^{54}$	310 days	gamma	Trace element distribution
Chlorine	$_{17}Cl^{36}$	4.4×10^{5} years	neg. beta positrons gamma	Electrolyte metabolism
	$_{17}Cl^{38}$	38.5 min	neg. beta gamma	
Copper	$_{29}Cu^{64}$	12.8 hours	neg. beta positrons gamma	Hematopoiesis Trace element utilization
Chromium	$_{24}Cr^{51}$	26.5 days	gamma	Blood volume determinations
Yttrium	$_{39}Y^{88}$	104 days	positron gamma	Intravenous colloidal therapy in reticuloendothelial neoplasms
	$_{39}Y^{90}$	[illegible] days	neg. beta	
	$_{39}Y^{91}$	[illegible] hours	neg. beta	

loaded at the same time They are then carried in a lead container to the Department of Radiology

Figure 26A 1 demonstrates the cutting and calibration arrangement The Au^{198} wire, encased in the inactive outer gold tubing is taken from the storage container and inserted into the central bore of a lead shield From this lead shield the encased Au^{198} wire can be extruded to a length that may be adjusted by a micrometer from 2 to 40 mm An Au^{198} of

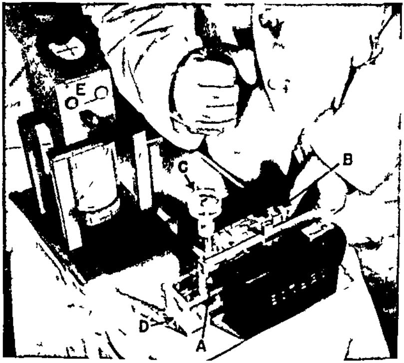


Fig 26A 1 Au^{198} seed cutter A Central bore through which Au^{198} is extruded B Calibrated handle to advance the wire the desired length C Cutting mechanism by forcibly pushing on the arm attached to the cutter shearing action is brought on the wire D Plastic container for seeds E Survey meter

this length is then cut off by pushing down the handle

Calculation of the dose in roentgens was mainly based on the Quimby or the Paterson Parker tables One mc of Au^{198} during total decay delivers 2 4 rhcm × 93 (average life in hours) = 223 r at 1 cm distance Conversion of the Quimby or Paterson Parker tables for use with Au^{198} may therefore be carried out on the basis of the relations

1 mc Au^{198} for total decay = 27 mgh radium

and

1 mgh radium = 0 038 mc Au^{198}

For conversion of radon tables the following relations may be used

5 mc of Au^{198} = 1 mc of radon and

1 mc of Au^{198} = 0 2 mc of radon *

CLINICAL USES

Two hundred and eight patients were treated with this type of gamma ray source between October 1, 1952, and June 30 1954 No appreciable differences have been noted clinically in the reactions to therapy with Au^{198} in comparison with Co^{60} radium and radon

Whether Au^{198} seeds should be used in preference to needles or nylon applicators containing Co^{60} or radium will depend largely on the clinical situation For example in tumors of the bladder or the gastrointestinal tract the permanent implantation of Au^{198} eeds will often be preferable to the use of needles that must be removed subsequently because of the long lived gamma ray emitters

This factor results from the relations of the figures for the total do e delivered at 1 cm For 1 mc of radon the total dose delivered at 1 cm is 133 (average life in hours) × 8 4 (rhcm/mc) = 1117 r For 1 mc of Au^{198} the figure is 93 (average life in hours) × 4 (rhcm/mc) = 23 r 3/1117 = 0

TABLE 26A 1 —METHODS OF APPLICATION AND TYPES OF TUMORS

Type of Tumor	*Number patients*	*Method of application*			
		Mold	*Intracavitary applicator*	*Permanent implant*	*Removable nylon implant*
Head and neck	86	5	3	35	43
Urinary tract	29	1	3	19	6
Female genitals	24	3	7	10	4
Skin	17	2	–	10	5
Hemangiomas	16	–	–	2	14
Breast	18	–	–	8	10
Gastrointestinal	14	–	3	10	1
Others	4	1	–	2	1
All tumors	208	12	16	96	84

they contain Important uses for Au^{198} seeds will also be found in those practices where many patients have to be treated on an out patient basis because of the paucity of hospital beds

In Table 26A 1 are shown the principal clinical categories of application in the first 208 patients classified according to the four methods by which the Au^{198} sources were used (1) molds (2) intracavitary applicators (3) permanent implants and (4) removable nylon implants Figures 26A 2 and 26A 3 demonstrate patients in whom radioactive gold was utilized

Radiogold (Au^{198}) Seeds in Molds

The long lived radioisotopes such as Co^{60} or radium are the usual choice for molds because no extra expense or labor is required in preparing these radioactive substances if they are available in the hospital However molds containing Au^{198} sometimes offer advantages over other gamma ray emitters because

1 Hospitalization or repeated visits of the patient are not necessary

2 Adjacent radiosensitive tissues can be protected effectively with lead shields

3 Recovery of the radioactive substances from the molds is not required

Radiogold (Au^{198}) Seeds in Intracavitary Applicators

Co^{60} or radium is the usual choice for intracavitary applicators However Au^{198} occasionally may offer advantages over other gamma ray emitters because

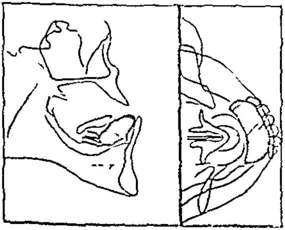


Fig 26A 2 Intraoral mold with Au^{198} wires and built-in protective lead shield combined with a permanent implant used for treatment of a squamous-cell carcinoma of the floor of the mouth in a fifty-year-old male on an ambulatory basis (From Henschke James and Myers [3] courtesy *Radiology*)

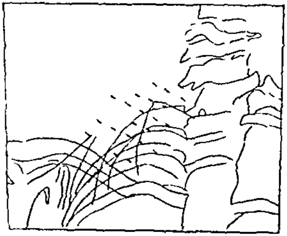


Fig 26A-3 Nylon implant with Au^{198} seeds used for treatment of a fibrosarcoma in right supraclavicular region There is uniform loading of the nylon applicators in a forty-two-year-old female for a dose of 6 000 r with remarkable clinical improvement (From Henschke James and Myers [3] courtesy *Radiology*)

1 Smaller tubes can be used than with radium

2 Adjacent radiosensitive tissues can be protected effectively by a lead shield

Radiogold (Au^{198}) Seeds in Permanent Implants

For permanent implants only short lived radioisotopes such as Au^{198} or radon can be used Au^{198} seeds for permanent implants have the practical advantage over radon seeds that seeds of uniform strength can be prepared immediately whenever the need for them arises This possibility was very valuable in 7 patients when a nonresectable tumor was encountered unexpectedly at surgery Usually the cutter in these cases was taken to the operating room and the seeds were cut and calibrated within a few minutes Advantage of the quicker preparation of Au^{198} seeds has also been taken in patients who were referred for consultation to the tumor conference and who were then implanted immediately following the recommendation of the conference In this way consultation and treatment were carried out in a single visit within a few hours

With present implantation technics the patterns of seed distribution in permanent implants are not as accurate as they are in removable nylon or needle applicator implants For this reason permanent implants are preferred over removable implants only if

1 Removable implants are difficult to carry out

2 Only short term palliation can be expected

Use of permanent implants when removable implants are difficult is most frequently carried out in intraabdominal tumors This is especially indicated in tumors in the depth of the pelvis such as carcinomas of the bladder and of the prostate Furthermore for abdominal tumors a removable nylon implant cannot be accurately prepared in advance because the shape and extent of the tumor are usually uncertain Finally in the abdomen removal of an implant is more hazardous because occasionally the withdrawal of needles or nylon applicators may cause bleeding

Use of permanent implants when only palliation can be expected often appears preferable to a removable implant because no preparation is required local anesthesia is often sufficient implantation is more quickly carried out no supervision of the patient during the implantation period is required and removal is not necessary

Although there has been considerable experience with permanent implants with radon seeds here it is very difficult to evaluate a possible difference in the therapeutic effect between Au^{198} seeds and radon seeds implanted permanently, because the variation in pattern is so great and because the accuracy of implantation is the decisive factor Appreciable differences due to the choice between Au^{198} and radon seeds have not been observed clinically

Radiogold (Au^{198}) Seeds in Removable Nylon Implants

In discussing the nylon technic it must be pointed out that the preparation of the nylon applicators requires time and skill Furthermore the technic of preparing nylon applicators to carry Au^{198} seeds is still in the developmental stage It is possible to use nylon tubing in a manner similar to that developed for the use of small cylinders containing Co^{60} by separating the Au^{198} seeds with aluminum spacers [9 11] However since the gold seeds have almost twice the diameter of the Co^{60} cylinders nylon tubing with larger internal diameter must be used for Au^{198} seeds This larger nylon tubing lacks the flexibility of the nylon tubing of smaller diameter used for Co^{60} In order to overcome this difficulty a flat very flexible nylon ribbon has been developed in which the seeds are firmly held without spacers This ribbon is even more flexible than the nylon tube used for Co^{60}

Nylon implants are preferred over needles for removable implants because they provide for (1) more accurate implantation (2) better individualization (3) more comfort to the patient and (4) decreased exposure to the operating personnel

multiplying mgRaeq with a factor of 1 5

For dose calculations the same tables and curves as for radium sources can be used since the dose distribution up to 5 cm from an Ir^{19} source in tissue is more or less similar to a corresponding radium source It is preferable that the dose rates from Ir^{19} be measured directly with a small scintillation crystal or a small Geiger counter

CLINICAL USES OF RADIOACTIVE IRIDIUM

From July 1 1954 to June 30 1957 253 patients have been treated with the small Ir^{192} sources directly by us and about 29,000 Ir^{19} sources have been supplied to personnel of other hospitals who have cooperated in the investigation of this radiation source

Ir^{19} Sources in Molds

Ir^{19} sources are preferred for molds and other surface applicators over radon and Au^{198} because they are more readily available due to the longer half life and because they are less expensive They are preferred over radium and Co^{60} because they are inexpensive enough to be disposed of with the mold, because protection during the preparation and the transportation of the mold is easier and because effective lead shields can be incorporated

Ir^{19} in Intracavitary Applicators

In many intracavitary applications the smaller diameter of the Ir^{19} sources compared with radium radon Co^{60} and Au^{198}, is an advantage One can place an unloaded tube with a central wire in a cavity e g in the esophagus urinary bladder urethra or rectum check the position roentgenographically then remove the wire and finally replace the wire quickly and accurately with a small nylon tube loaded with the Ir^{19} sources In urinary bladder applications drainage of urine is no problem since the small nylon tube does not obstruct the lumen of the catheter Ir^{19} sources are usually not removed from intracavitary applicators but are simply disposed of with the applicators after use This facilitates the use of the sources in a number of applications e g in small plastic balls for the pack ing technic and in intracavitary applicators made from dental compound

Ir^{192} in Removable Implants

Through the use of Ir^{19} sources the nylon implantation technic is becoming available to many hospitals With the Ir^{19} sources preloaded in nylon tubes by the commercial supplier there is no need for any special service in the hospital The handling is simpler and safer than with radium and radon and the container with the loaded tubes can be kept sterile in a bag and ready for use at any time

Several modifications of the basic nylon implantation technic have been developed that permit its use in tumors in any location Thus it has become the only technic used for removable implants in our practice While most nylon implants are left in place for about one week some implants have been left in position for several weeks

Ir^{192} in Permanent Implants

Ir^{19} sources offer intriguing possibilities for cancer therapy in the form of permanent implants In this application half of the total dose is delivered in about ten weeks Such continuous long time irradiation has not been possible with x ray therapy or with radium or radon On the basis of radiobiologic experiments and of experiences with protracted x ray therapy it appears that long time continuous low intensity irradiation with permanently implanted Ir^{19} sources will offer an effective form of cancer irradiation

Permanent implantation of the long half life Ir^{19} sources offers the following important advantages over permanent implantation of radon or Au^{198} sources (1) Ir^{19} sources in suitable strength can be stored for a prolonged period (approximately one month) (2) Since the gamma activity of the Ir^{19} sources at the time of implantation can be about twenty times less for the same total dose exposure to operating room and nursing personnel is much lower and larger volumes can be safely implanted (3) Ir^{19} is cheaper

Compared with other isotopes suggested for permanent implantation—radioactive tantalum (Ta^{18} half life 118 days Cohen 1955) and radioactive chromium (Cr^{51} half life 26 5 days Myers 1956)—the Ir^{19} sources can be produced more economically However the final choice of a radioisotope for permanent

implantation will depend on careful clinical studies of the therapeutic effectiveness

As outlined in the preceding chapter permanent implants with radioisotopes have definite advantages especially for intrathoracic and intraabdominal neoplasms and for palliative treatment With the usual implantation methods for radon and Au^{198} sources however a satisfactory distribution in a permanent implant is rarely accomplished In an effort to improve the accuracy of permanent implantation two methods have been developed In the first the same nylon tubes with Ir^{192} are used as for removable implants Essentially the same implantation technics are employed but at the end the nylon tubes are cut where they come to the surface and are allowed to slip back into the tissue In the second method unloaded hollow needles 15 cm long are first placed in and around the tumor The implanted volume is determined by measuring with a ruler the separation of the needles and their outside length The number of sources for the desired tumor dose is now figured

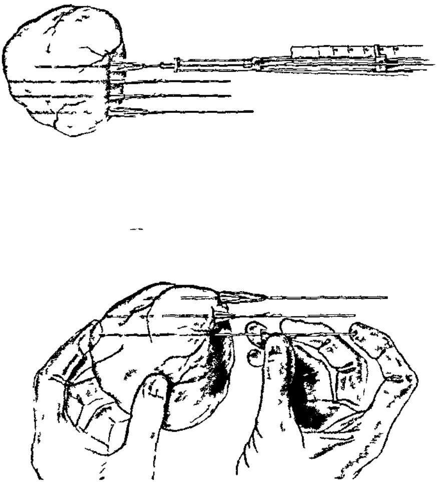


Fig 26B-1 Technic for permanent implantation of radioisotope seeds (*Upper*) Unloaded hollow needles are first placed in and around the tumor (*Lower*) Next a special instrument with depth gauge is attached to each needle in turn With it the desired number of radioisotope sources are introduced one after another through each needle and properly spaced in the tissue

Next a special instrument with depth gauge is attached to each needle in turn With it the desired number of radioisotope sources is introduced and properly spaced in the tissue

This implantation technic together with the use of Ir^{192} sources has made it possible to implant large volumes with reasonable speed and accuracy The method has been used up to June 30 1957 in 58 patients most of them with nonresectable intrathoracic and intra

Fig 268 2 Example of a permanent implant with Ir^{19} sources A forty-eight year old woman with cancer of the cervix which had recurred after hysterectomy and x ray therapy and caused severe pain and swelling of the right leg and marked right hydronephrosis as shown by radiographic examination Exploration showed nonresectable tumor masses and 76 Ir^{19} sources were permanently implanted through 20 needles The patient became free of symptoms within one month and the hydronephrosis disappeared

abdominal tumors No serious side reactions have been observed and good tumor regression has been the rule Much more experience is of course required before permanent implantation with Ir^{19} sources can be evaluated and it is too early to recommend this technic for general use On the basis of our preliminary experience this technic shows promise of becoming an effective approach in dealing with most nonresectable cancers that have not metastasized widely

EDITORIAL NOTE

The careful distribution of the radiation sources within the tumor as developed by Doctor Henschke is most important in obtaining uniform irradiation regardless of the characteristics of the radioactive isotope used. The injection of a liquid radioactive isotope such as radioactive gold or chromic phosphate offers an extremely poor method of obtaining uniform dosage

The technic develped by Dr Joseph Greenberg and his associates incorporates yttrium 90 within tissue soluble plastic filaments (methyl cellulose) The methyl cellulose is absorbed leaving a fine linear disposition of the radioactive yttrium within the tumor tissue This technic offers another means of obtaining uniform dosage of interstitial radiation sources [1]

CHAPTER 27

The Clinical Application of Small Sources of Radioactive Cobalt

Joseph L Morton
and
George W Callendine, Jr

Radioactive isotopes can be used in the treatment of cancer either as substitutes for radium and/or radon or in technics that are superior to those with radium

Of the available radioactive isotopes radio active Co^{60} may serve as a replacement for radium Natural cobalt (Co^{59}) is a metal similar in many respects to iron It may be alloyed with other metals drawn into wire or machines and the cobalt itself is magnetic Co^{60} is made conveniently in nuclear reactors from the preformed natural cobalt by the process whereby Co^{59} captures a neutron The equation for this reaction is $Co^{59} + n = Co^{60}$ Cobalt 60 decays with a half life of 5 25 years by beta emission accompanied by 2 gamma rays in cascade The beta particles have a maximum energy of 0 3 mev while the two photons have energies of 1 17 mev and 1 33 mev

As in the case of radium the desirable portion of the radiations from Co^{60} for thera peutic applications is the gamma rays The relatively weak beta particles are much easier to filter out than are those beta particles from radium in equilibrium with its decay products The maximum range in tissue of the Co^{60} beta particles is 0 8 mm and the maximum range in stainless steel is 0 1 mm Therefore the beta particles can be filtered out with thin

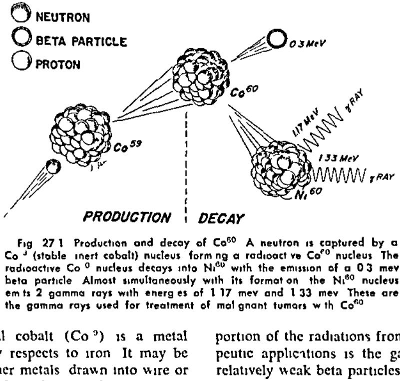


Fig 27 1 Production and decay of Co^{60} A neutron is captured by a Co^{59} (stable inert cobalt) nucleus forming a radioactive Co^{60} nucleus The radioactive Co^{60} nucleus decays into Ni^{60} with the emission of a 0 3 mev beta particle Almost simultaneously with its formation the Ni^{60} nucleus emits 2 gamma rays with energies of 1 17 mev and 1 33 mev These are the gamma rays used for treatment of malignant tumors with Co^{60}

layers of low scattering material

The absorption coefficients for both types of gamma rays of Co^{60} are similar in bone They are also similar in the soft tissue For practical purposes the radiations are considered monoenergic (monochromatic in wavelength) and the possibility of heterogeneous irradiation—with the associated increased absorption for lower energy components—is eliminated

Because of the tendency of the cobalt metal to be chemically active under continued handling it is desirable to alloy the cobalt so that inert chemical properties result The source alloy is a hard chemically resistant (Stainless) alloy manufactured by the Haynes Stellite Company of Kokomo, Indiana This alloy (Haynes No 25) is approximately 50 per cent cobalt and the alloying components are chromium tungsten nickel manganese, iron silicon with traces of carbon phosphorus and sulphur None of these alloying components is present in sufficient quantities or has sufficiently large neutron cross sections to produce any important heterogeneous radiations and so the irradiated alloy is effectively a Co^{60} source

After the sources are preformed as desired,

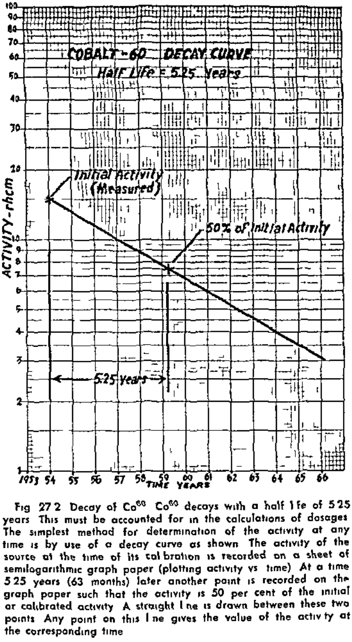


Fig 27 2 Decay of Co^{60} Co^{60} decays with a half life of 5 25 years This must be accounted for in the calculations of dosages The simplest method for determination of the activity at any time is by use of a decay curve as shown The activity of the source at the time of its calibration is recorded on a sheet of semilogarithmic graph paper (plotting activity vs time) At a time 5 25 years (63 months) later another point is recorded on the graph paper such that the activity is 50 per cent of the initial or calibrated activity A straight line is drawn between these two points Any point on this line gives the value of the activity at the corresponding time

they are nickel plated either before or after irradiation in the reactor by a chemical deposition process (called the KANIGEN process) developed by the Kanigen Division of the General American Transportation Corporation This remarkably chemical resistant and nonporous nickel sheath is then overplated with chromium for abrasion resistance Thus one has a chemically resistant cobalt base plus a very resistant nickel sheath and the final protection of chromium

The specific activity—amount of activity per gram of material—can be varied almost at will with Co^{60} simply by securing different neutron irradiation times in the nuclear reactor For example small cylinders of cobalt of 0 1 cm diameter by 0 1 cm long have been irradiated to a strength of more than 150 rhcm The same center possesses cylinders of 0 3 cm diameter by 1 0 cm and of strength only about 50 rhcm The large cylinders are 90 times as massive as the smaller ones but are only one third as active making a difference in specific activity of 270 Greater ranges of specific activity can be achieved if desired This makes Co^{60} an extremely versatile source

The size of the sources is dictated by the use to be made of them For large cavitary applications sources may be in the form of beads several millimeters in diameter For rigid needles similar to radium needles sources may be lengths of wire of diameters as small as 0 2 mm For use in flexible tubes individual sources 0 7 mm in diameter by 3 0 mm long are used

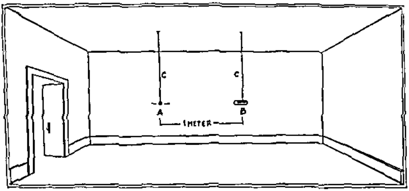


Fig 27-3 Calibration of Sources The source to be calibrated (A) is positioned so that it is at least 1 meter away from the nearest scattering material This can be accomplished by suspending the source by a fine thread (C) The center of the chamber of an electroscope (B) is positioned exactly 1 meter from the center of the source The chamber should also be at least 1 meter from any scattering material

The electroscope has been previously calibrated so that its discharge rate is known in milliroentgens per hour This can be accomplished by using a known source of radium a calibrated source of Co^{60} or by having the electroscope calibrated by the National Bureau of Standards or by a qualified physicist

The rate of the discharge of the electroscope in milliroentgens per hour is determined for this geometry The source is then removed from the vicinity and the rate of discharge of the electroscope again determined (this is the background rate) This background rate is subtracted from the previously secured rate to determine the net rate of discharge due to the source of activity The units of this rate are mrhm (milliroentgens per hour at 1 meter) For the medical viewpoint it is desirable to convert to roentgens per hour at 1 cm

Conversion to rhcm (roentgens per hour at 1 cm) is carried out by simply multiplying the mrhm value by 10 Actually one multiplies by 10 000 $(100\ cm)^2$ and divides by 1 000 (number of milliroentgens per roentgen) but the net result is to multiply by 10 The value of the activity in rhcm is the working unit for therapy calculations

DOSAGE MEASUREMENT

Sources received from Oak Ridge directly are uncalibrated Calibration is therefore necessary upon receipt and can be accomplished by sending a sample source to the National Bureau of Standards by having a competent

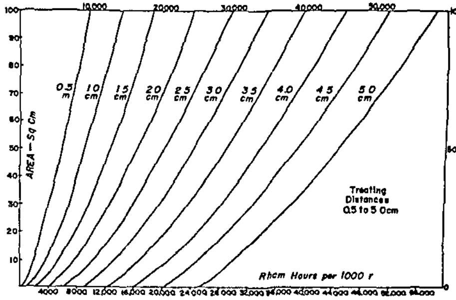


Fig 27-4 Paterson and Parker mold therapy graph converted for Co^{60} The graphs as originally presented define the amounts of radium to be used for various areas and treating distances These charts have been converted by changing the unit of source strength from mg to rhcm (from the relation 1 mg radium corresponds to 8 4 rhcm when filtered with 0 5 mm Pt) This surface mold graph is used in a fashion similar to the original and all distribution rules set up by Paterson and Parker must still be observed

physicist come in to calibrate the sources or by performing the calibration oneself A simple and satisfactory method is to place a quartz fiber electroscope a distance of 1 m from the source to be measured (in the absence of other radioactivity) and note the discharge rate As the working unit for therapy is the roentgen the discharge rate of the electroscope is calibrated in *milliroentgens per hour* The source strength is thus estab

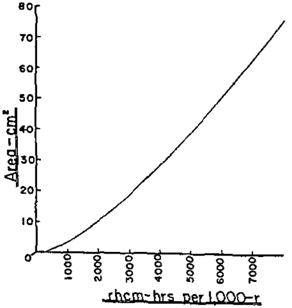


Fig 27 5 Paterson and Parker planar implant graph converted for Co^{60} This graph was constructed in a fashion similar to that in Figure 27-4 The graph is used in conjunction with the theory developed by Paterson and Parker

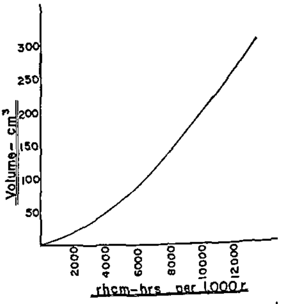


Fig 27-6 Paterson and Parker volume implant graph converted for Co^{60} This graph was constructed in a fashion similar to that in Figure 27 4 It is to be used in conjunction with the theory developed by Paterson and Parker

lished in milliroentgens per hour at a distance of 1 m and the abbreviation for this unit is mrhm This unit is then arithmetically converted to one that describes the dose rate 1 cm from the source (assuming a point source) The converted unit is the rhcm (roentgens per hour at a distance of 1 cm from a point source) The rhcm is the working unit of source strength For therapy it is much more meaningful and practical than the millicurie which defines *the rate of disintegration*

Because of the half life of 5 25 years for the Co^{60}, the continual decay of the sources must be taken into consideration The easiest method of observing this decay is a graphic one in which the activity is plotted as a straight line function of time on semilogarithmic graph paper such that a time interval of 5 25 years (63 months) results in a reduction in intensity of one half

Recalculations have been made for Paterson Parker dosage tables These tables express the dose in rhcm hours per *1 000 roentgens* instead of *mg hours per 1 000 roentgens* so it is obvious that the only change made is in the unit of source strength When it is realized that *rhcm* is a more universally applicable unit of measure than *mg* or *mc* then the *rhcm* will be used by the therapist to describe radiation from any source whether it be radium radon Co^{60} Au^{198} or an x ray tube For any simple application the dose expected a *different points can easily be approximated* by dividing the activity in rhcm by the square of the distance of the point from the activity This is a simple inverse square law calculation

ISODOSE APPLICATIONS

The Paterson Parker schedules were calculated on the theoretic basis of radioactive fluids Simplifying approximations were then made to facilitate the use of radium needles at a time when no other radioactive material was available With the advent of other radio isotopes (Co^{60} Au^{198} Ir^{192}) many of these approximations are no longer necessary It is possible through the use of multiple small sources of radioactive fluids more nearly to approximate the original ideal of radioactive fluid Therefore multiple small sources should give more satisfactory radiation patterns

In practice a type of grid therapy results from the use of small sources Regions of sharp local overdose occur in the immediate vicinity of the sources and these are kept isolated from each other by the placement of sources In general each source is between 0 6 cm and 1 0 cm from adjacent sources Successes in *large volumes can only be* accounted for by some grid effect not unlike that of the massive overdosage with grid x ray therapy and to the use of as little metal in the tissues as possible for there is a definite clinically recognizable erythema about wire retaining sutures metal buttons in contact with the skin etc

The small individual sources of Co^{60} and the wide range of specific activities available permit extensive flexibility of application Not only can the Paterson Parker theories be more closely approximated for the relatively simple configurations with which they deal but any complex configuration (dumbbells wedges etc) can be irradiated uniformly simply by proper positioning of the sources The dose time relationship also can be varied at will for any given configuration of needles or tubes containing activity

ENCAPSULATION

The technics of encapsulation of the sources are unlimited All the technics employed with radium may be utilized In addition many others may be added because of the physical *nature of the sources (metal wire or pieces)* Rigid needles may be made by encapsulating the Co^{60} in stainless steel semirigid needles in soft stainless steel alloys or hard aluminum alloys and flexible linear sources or threads in nylon tubing

CLINICAL APPLICATIONS OF RADIOACTIVE COBALT

Intracavitary

BLADDER

Existing technics utilizing small sources of radioactivity at the center of catheters may be extended with the aid of Co^{60} For irradiating the entire wall surface of the bladder a Foley catheter is inserted into the bladder and the balloon *inflated A very small high specific* activity Co^{60} cylinder (0 1 × 0 1 cm 150 rhcm) or group of cylinders is positioned in a

A

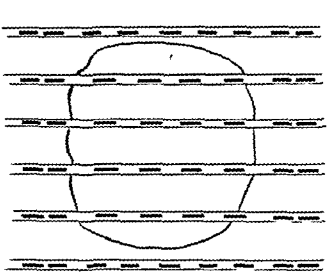


Fig 27 7A Small cylindrical sources facilitate uniform dose distributions where location of the tumor affords only limited access An advantage of the smallness of the cylindrical sources of Co^{60} (0 05 cm diameter by 0.3 cm long cylinders) is realized when they are considered to be effective point sources and varied in position along the needle in response to an anatomically imposed deformation of the standard needle pattern By such an artifice uniform irradiation can be more nearly secured with irregularly placed needles

Such a differential loading is not new with fixed applicators (needles) Fabrication of individual linear applicators for each tumor is in our opinion the only justifiable procedure in a condition as lethal as cancer We believe that our results would justify the expense of the method The causes of failure can then be more accurately assessed since having laid the bugbear of dosage in the tumor the failure can be attributed to an error of judgment as to location or to an unusually autonomous tumor that does not respond to irradiation

Two common examples are illustrated Figure 27 7A shows the sources arranged to provide a uniform irradiation pattern for a rectangular planar implant with uncrossed ends The same effective irradiation that would be secured by crossing the ends is made possible by positioning extra small sources at the end of each line of source This is a very convenient loading for frequently it is either inconvenient or impossible to cross one or both ends with linear sources as prescribed by the Paterson and Parker theory

B.

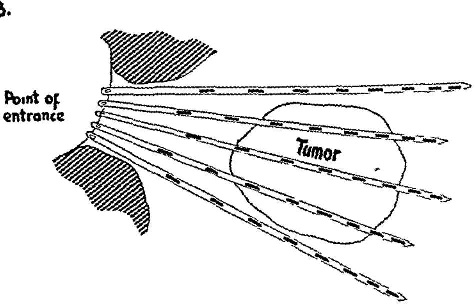


Figure 27 7B Indicates the application of diverging or converging needles and an extension of this loading can be employed in a truncated cone or pyramid As illustrated a dose leveling effect is secured by varying the spacing within the needle in a manner reciprocal to the distance between the needle axes This is clinically more tolerable than overdosage or underdosage over a larger area or volume

small nylon tube so that the nylon tube can be inserted in the catheter after positioning of the catheter to insure that the activity will be at the center of the bladder The outside of the nylon tube is approximately 0 15 cm, which will not obstruct the catheter thus permitting free drainage Dose rates of 60 r/hr are easily achieved on the wall of a 5 cm diameter sphere around the source and larger doses can be provided (Figure 27 18) To irradiate the neck of the bladder more than the remainder the Co^{60} pieces are loaded into the nylon tube to be nearer the bladder neck after the nylon is inserted into the catheter

UTERINE FUNDUS

The uterine fundus is most effectively filled with small spheres threaded on a string These spheres may be solid cobalt alloy or steel or plastic loaded with discrete sources Either way the technic which is basically similar to the Heyman and other packing technics becomes valuable for two reasons (1) spheres of any size and activity may be chosen, and (2) the insertion takes only a matter of 30 to 50 seconds which means the operating surgeon receives insignificant irradiation during the procedure

BRONCHUS

The high specific activity small source size cobalt again may be used in special bronchial applicators The applicators may be constructed so that an air passage completely encircles the source permitting the patient to breathe while being treated This is also useful for bleeding recurrence in the bronchial stump

OTHER USES

Other applications where radium is used in cavitary applications can be similarly treated with cobalt

Cervix Uteri

TANDEM AND COLPOSTAT

Traditional treatments utilizing tandems and colpostats are carried out with cobalt as with radium Owing to the low initial investment required it is practical to secure enough Co^{60} to load a complete series of tandems and colpostats Reloading is therefore not necessary and different sizes are drawn from the available stock as required Constructing the tandems and colpostats from stainless steel and permanently imbedding the activity permits continuous sterilization The tandems and colpostats are stored in a pan filled with instrument Zephiran chloride solution which

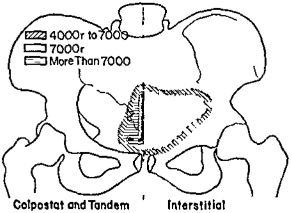


Fig 27 8 Dosage contours for two methods of treatment of carcinoma of the cervix uteri Treatment of carcinoma of the cervix uteri with tandem and colpostat is inadequate for other than early localized lesions Improvements have been made in treating larger volumes of tissue by interstitially implanting needles into the parametrium These methods have had the limitation that the needles are implanted free hand and accurate placement is extremely difficult

Figure 27 8 shows the relative treatment dosage contours possible with the two methods In contrast with the high intensity regions near the tandem and colpostat for any appreciable depth dose to the parametrium a relatively uniform dose is secured throughout the entire implanted volume with the interstitial technic

The interstitial technic becomes more practical if the needles are inserted through a guide template which avoids the errors in distribution inherent in free hand insertion

in turn is placed in the cavity at the center of a lead spheroid the top of which can be retracted for access to activity

Tandems stocked range in 1 2 cm increments from lengths of 0 9 cm to lengths of 8 1 cm and are all 3/16 inch in diameter They are bent slightly so that they curve anteriorly Colpostat lengths range in 1 cm increments from 3 cm to 6 cm The tandems are provided with a tapped hole at their base The bases of the tandems fit into the colpostat and provision is made for affixing the tandem to the colpostat with a small stainless steel screw Insertion rods consist of threaded rods which fit into tapped holes in the tandem

and/or the colpostat After the applicator is packed in place these rods conveniently screw out without disturbing the pack The applicators have been loaded so that the desired dosages will be achieved in approximately 5 days (120 hours) irradiating time for any pelvic examination radiographic examinations of the pelvis with contrast material in the bladder rectum and vagina (a p and lateral stereographs laminagrams etc) A lucite jig can then be designed to fit in the vagina through which guide holes are drilled These

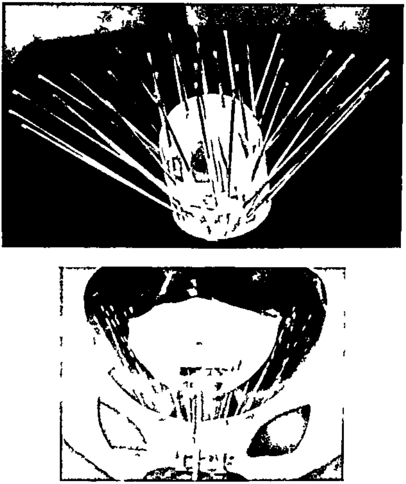


Fig 27 9 Co^{60} implantation of cervix uteri and parametrium with rigid needles (Upper) A photograph of an applicator used in the treatment of carcinoma of the cervix with Co^{60} The lucite guide cylinder fits into the vagina and the needles are inserted one by one through predrilled holes until the pattern is complete A block of tissue approximately 4 × 7 × 12 cm is treated uniformly to a dosage of 7 000 r in 1 week

(Lower) Radiographic image showing the actual placement of the needles in the pelvis in a typical case as well as the positions of the individual Co^{60} sources in the needles

colpostat in combination with tandems of length 3 3 cm or longer

INTERSTITIAL NEEDLES

It is possible to extend the volume of tissue adequately irradiated with tandem colpostat type applicators with the aid of the precisely placed linear interstitial sources Preoperative work up of the patient consists of precise guide holes permit needles containing the radioactive Co^{60} with predetermined loadings to be accurately positioned according to a planned theoretic pattern The placement is accurate to within 0 2 cm at the tips of the needles (the point of greatest deviation) when all needles are pushed to their predetermined depths Dosages given within the implanted volume are approximately 7 000 r in one week

Additional tumor outside the irradiated volume as defined by the needle pattern can be treated simultaneously. Laparotomy is performed at the time of insertion of the rigid needle pattern and Co^{60} nylon threads (nylon tubing containing cylinders of Co^{60}) are sewn

Means of Application

RIGID NEEDLES

Co^{60} can easily be loaded into rigid needles and used in a manner similar to radium needles. Owing to the weak beta particle, gold

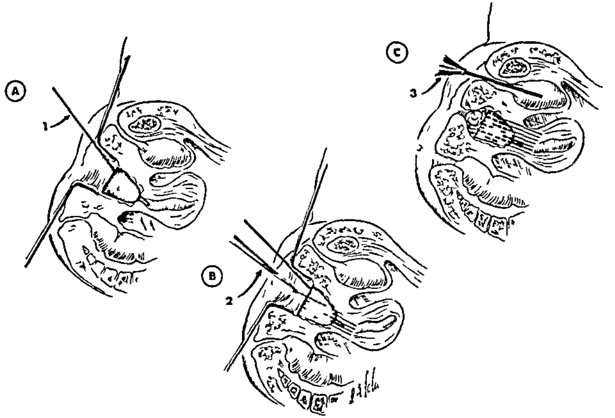


Fig. 27.10. Technic for interstitial implantation in treatment of carcinoma of the cervix uteri. Following a preoperative study of the pelvis by the gynecologist and the radiologist, a needle pattern is chosen to conform with the basic theories of Paterson and Parker. Holes are drilled in a lucite cylinder at angles which, when rigid needles are passed through them, facilitate this needle pattern. Rigid needles are loaded with small cylinders of radioactive Co^{60} in such distributions as prescribed. At operation, a ⅛-inch diameter rod (1) is screwed in the base of the lucite cylinder and the cylinder is positioned in the vagina. A schematically illustrates this. A small lucite tip is noted on the end of the cylinder that positions in the cervical canal.

After positioning of the lucite cylinder, the needles are inserted singly through their predetermined guide holes to specified depths as indicated in B. A modified right-angle gallbladder forceps (2) is used to hold the needles for this insertion. A lucite plate is positioned to retain the needles at the predetermined depths.

The urinary bladder and rectum are checked after implantation of the pattern for possible puncture by needles. The vagina is packed with gauze. A scintillation probe counter (3) is also used to check the dose rate in the urinary bladder and rectum (C).

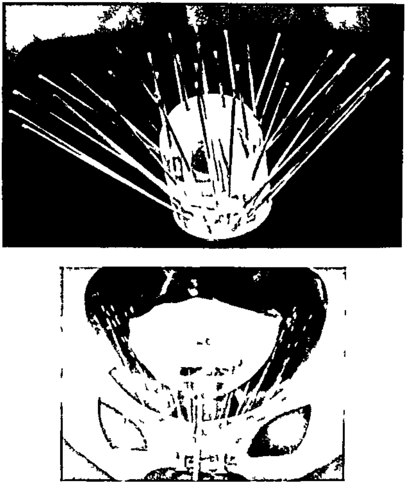
into the regions not covered by the needles. This is performed under direct vision and is possible as the needle pattern is so designed that the tips of the needles are near enough to the peritoneum to be discerned at laparotomy. This technic is especially valuable for extensions along the pelvic wall and along the lymph node chains.

or platinum is not required as shielding material and hyperchrome stainless steel works very satisfactorily.

SEMIRIGID NEEDLES

In similar manner Co^{60} can be loaded into less rigid needles and used in many applications. Some of the materials used satisfactorily

and/or the colpostat After the applicator is packed in place these rods conveniently screw out without disturbing the pack The applicators have been loaded so that the desired dosages will be achieved in approximately 5 days (120 hours) irradiating time for any colpostat in combination with tandems of length 3 3 cm or longer



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(*Lower*) Radiographic image showing the actual placement of the needles in the pelvis in a typical case as well as the positions of the individual Co^{60} sources in the needles

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Additional tumor outside the irradiated volume as defined by the needle pattern can be treated simultaneously Laparotomy is performed at the time of insertion of the rigid needle pattern and Co^{60} nylon threads (nylon tubing containing cylinders of Co^{60}) are sewn into the regions not covered by the needles This is performed under direct vision and is possible as the needle pattern is so designed that the tips of the needles are near enough to the peritoneum to be discerned at laparotomy This technic is especially valuable for extensions along the pelvic wall and along the lymph node chains

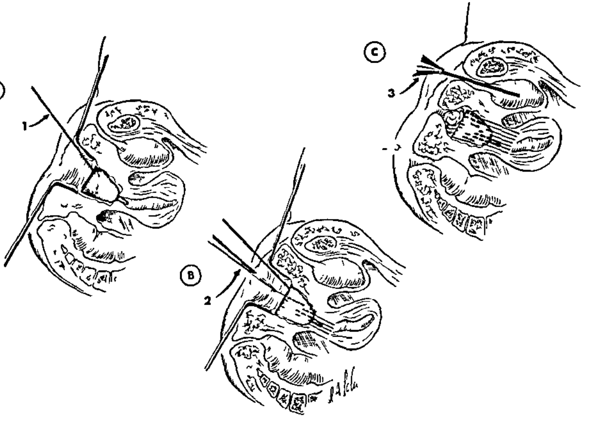

Fig 27 10 Technic for interstitial implantation in treatment of carcinoma of the cervix uteri Following a preoperative study of the pelvis by the gynecologist and the radiologist a needle pattern is chosen to conform with the basic theories of Paterson and Parker Holes are drilled in a lucite cylinder at angles which when rigid needles are passed through them facilitate this needle pattern Rigid needles are loaded with small cylinders of radioactive Co^{60} in such distributions as prescribed At operation a ⅛ inch diameter rod (1) is screwed in the base of the lucite cylinder and the cylinder is positioned in the vagina A schematically illustrates this A small lucite tip is noted on the end of the cylinder that positions in the cervical canal

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The urinary bladder and rectum are checked after implantation of the pattern for possible puncture by needles The vagina is packed with gauze A scintillation probe counter (3) is also used to check the dose rate in the urinary bladder and rectum (C)

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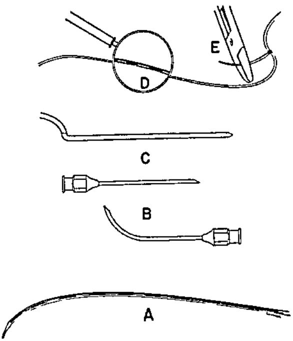
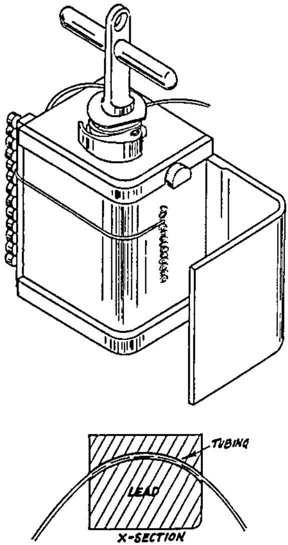


Fig 27 11 Apparatus for implantations with nylon threads Various types of applicators and guide needles are indicated in left figure A flexible nylon threads —nylon tubing containing Co^{60} cylinders B curved and straight grooved guide needles C rigid tubing containing Co^{60}; D magnification of nylon thread with centimeter rule the darker segments are the 3 mm long Co^{60} cylinders E curved and straight guide needles

The lead nylon thread carrier is sketched in the right figure The active portion of the nylon threads lies inside the lead shield while the inactive portion is fastened outside the lead In practice the inactive portion on one end (called the leader) is approximately 1 meter long and is drawn into the tumor while all activity remains safely within the lead After all leaders for a given implant are positioned the activity is then drawn into place requiring a minimum of exposure to the operator (From James Williams and Morton [5] courtesy *Surgery*)



in this connection are soft alloys of stainless steel hard alloys of aluminum and gold (The last is not entirely satisfactory owing to the high scattering cross section of the gold) Typical applications where this type of linear source is indicated include the hard palate Needles are passed from the hard palate against the bone where they bend as much as is necessary to assume a continuous curve into the soft palate

FLEXIBLE THREADS

Spacing small cylinders of Co^{60} (0 3 cm long) inside nylon tubing (either with or without inert separating spacers) at predetermined distances apart provides versatile and practical linear source of radioactive material These nylon tubes loaded with Co^{60} (or other isotopes) are called nylon threads They are flexible and are used in any interstitial application Ease and rapidity of insertion excellent implantation patterns satisfactory patient tolerance and comfort during the implantation period and low dose to the surgeon at implantation (less than 25 per cent of the dose for a similar implant using radium needles) are a few of the advantages realized when nylon threads are used In practice the threads are made up with the activity within 20 cm of one end of a nylon tube approximately 100 cm long with the long inactive portion of the tube functioning as a leader At implantation long inert rigid or semirigid needles are used to serve as guides for tumor implantations after drawing the proposed pattern on the surface of the tumor with dye These needles are inserted through the tumor

at the precise positions selected for the activity After all needles are positioned satisfactorily for the implant the leaders are threaded onto the eyes of the needles and pulled into place, with the radioactive portion of the threads still remaining in a lead container placed on a table adjacent to the operating table Upon the satisfactory placement of all leaders the active portions of the threads are drawn into place and fastened with buttons *It is observed that the placement is* more accurate as there is no threat to the operator caused by fear of radiation exposure In cases where the tumor requires surgical exposure (pelvic nodes etc) the leaders of the threads are brought out through stab wounds to facilitate removal of the threads after the desired irradiation period

One of the most effective uses of the Co^{60} nylon thread is as an adjunct to cancer surgery In those patients whose cancer tissue cannot be totally excised radiation can enhance the possibility of a cure Co^{60} nylon threads are well suited to this type of application Non excisible portions of tumor are usually irregular in shape and the flexibility of the nylon permits better implantation than rigid needles

They are especially valuable in inoperable malignant tumors—inoperable because of inaccessibility of site nearness to large vessels

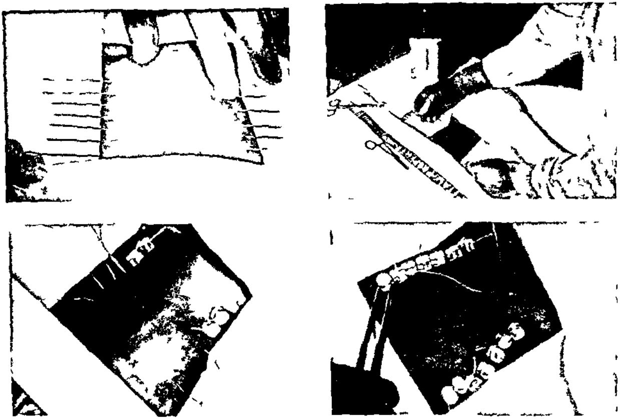


Fig 27 12 Nylon implantation technic—neck node The technic used in implanting nylon threads loaded with Co^{60} is demonstrated in a typical neck node application (*Top left*) The rigid guide needles are positioned after the treatment plan is determined Six needles are shown in place through the tumor and the seventh is being positioned After all guide needles are positioned to the satisfaction of the operator the lead shielded container containing the nylon threads is brought up near the operating site after sterilization in instrument Zephiran and the inert leaders of the threads are drawn into position (*Top right*) The nylon is threaded through the eye of the needle and drawn through During this operation the active portions of the theads—those portions containing the radioactive Co^{60}—remain in the lead shielded container

The active portions of the threads are then drawn into position in the tumor (*bottom left*) After positioning Lucite buttons are attached to the threads fixing their positions This figure shows two threads drawn in with buttons attached four with the leaders positioned and one being drawn in The dark sections of this thread are the small cylinders of radioactive Co^{60}

(*Bottom right*) The completed implant with the last button being positioned and the thread locked in place Since the threads are secured at both ends they will not travel during the treatment period After the desired treatment the buttons are removed and the threads withdrawn

bone, or regions previously irradiated to the point of tolerance They provide the surgeon at the time of operation with a readily available method of heavily irradiating deeply seated residual tumor

MOLDS

Mold therapy can be as conveniently carried out with Co^{60} as with radium or radon

size of the catheter was a welcome relief for irrigation and patient management Construction of the nylon tube obdurator is simple if telescoping nylon tubes are employed In Figure 27 18 *A* is the radioactive cobalt source, a plated cube 1 mm in diameter More than one cube can be used if desired Each cube is approximately 150 rhcm *B* is the outer nylon tube *C* is the inner nylon tube which

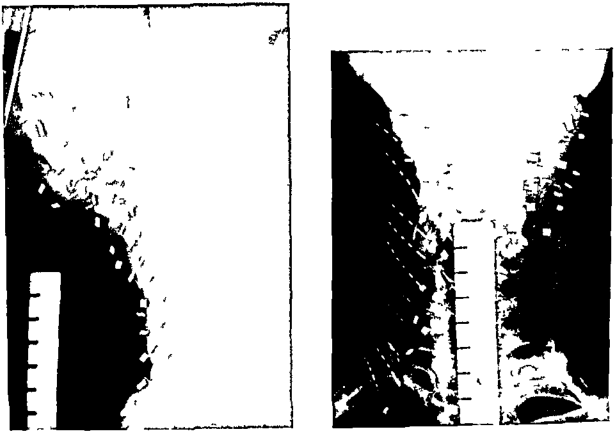


Fig 27 13 Implant of neck with nylon threads The lateral view (*left*) and the a p view (*right*) of a typical neck implantation with Co^{60} nylon threads The lateral neck is implanted with a planar pattern while a volume implantation is simultaneously carried out in the sub mandibular region A centimeter rule is placed on the drawings to show the relative sizes

FOLEY CATHETER WITH COBALT INSERT

The two lumen catheter has been abandoned as there is a great tendency for plugging of the urinary stream The active insert is carried in a small nylon tube which has a nylon obdurator The inner ends of the nylon tube and obdurator are closed by heat The length is chosen so that the catheter can be inserted and adjusted without difficulty The nylon tube containing the radioactive cobalt is then inserted a predetermined distance to center at the center of the inflated balloon The additional lumen

serves to hold the cobalt in the end and *D* is the Foley catheter

EVALUATION OF THE APPLICATION OF RADIOACTIVE COBALT

Statistical evaluation cannot be employed owing to the variation between individual patients and in the radiation technics employed Our studies were initiated in 1948 and the number of patients treated (406) is not large enough to be statistically significant Many of the treated patients have not been

Fig 27.14 Nylon implantation of pelvic node. A-p and lateral views of the nylon implant of a pelvic node. The patient was laparotomized and ten threads were sewn into the node with a curved cutting needle attached to the leaders. The leaders were brought out through the abdominal wall through a stab wound with the other end of the thread cut short and remaining within the pelvis. The incision was closed after implantation. Following delivery of the desired irradiation the threads were easily pulled out through the stab wound approximately one week later.

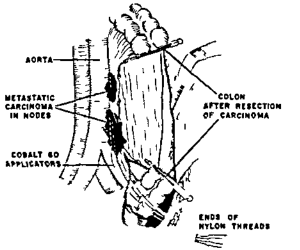


Fig 27.15 Co^{60} nylon threads in place in metastatic adenocarcinoma in para-aortic lymph nodes from cancer of the sigmoid colon. Loose ends of the threads (leaders) are brought out through abdominal wall stab wound for later removal. (*From James Williams and Morton [5] courtesy Surgery.*)

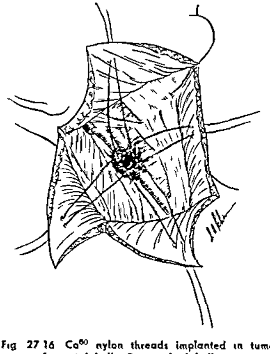


Fig 27.16 Co^{60} nylon threads implanted in tumor invasion of carotid bulb. Patient had bulky metastatic carcinoma in the neck. Neck dissection was performed but residual tumor was found to be invading the carotid bulb. This residuum was then implanted with radioactive cobalt as indicated. The leaders were brought out through stab wounds and the incision was closed. The threads were pulled out after the desired irradiation. This patient is still alive and free of cancer after 3.5 years. (*From James Williams and Morton [5] courtesy Surgery.*)

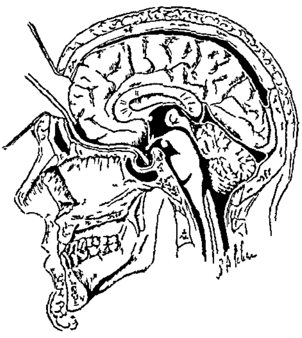


Fig 27 17 Internal irradiation of pituitary tumor J D a forty nine year-old lawyer was totally incapacitated from Cushing s syndrome resulting from a chromophobe adenoma of the pituitary gland The sella turcica was enlarged to about 2 5 cm in diameter and the patient had *not been improved* by 27 x ray treatments given at another hospital

Using a frontal approach to the pituitary region the center of the tumor was then aspirated The fossa formed served to hold a cobalt applicator fastened in the end of a soft rubber tube This remained in the center of the sella turcica The rubber tube extended out to the dura to serve as a drain The small cobalt applicator measured 331 rhcm which gave a 6 000 r dose to the surface of the sphere 2.5 cm in diameter at the end of 27 hours This method was employed because of the previous irradiation and because of the need for vigorous control of this apparently secreting pathologic clear-cell tumor and it is believed to be safer than a more thorough exenteration of the pituitary fossa The tube was withdrawn at the end of 27 hours without difficulty This man has had an apparently complete recovery and is able to engage in active practice as a lawyer He is on a small supporting dose of cortisone

followed long enough to draw valid conclusions

The effect on bone is unusually mild either because of uniformity of the small sources or a combination of the technic employed plus the natural transparency of bone to rays of this intensity At no time has necrosis of bone been without logical explanation such as recognized overdose infection or invasion by tumor We believe that 7 000 RLP is safe for bone

An effective point source applicator is made possible by the use of small Co^{60} sources At the present time we are using applicators 1 mm in diameter, plated and up to 150 rhcm strength In the future we plan to employ Haynes Stellite Alloy Number 25, with the above plating This has undergone rigorous tests by us and others and gives no contamination for such souces (see AEC Progress Report) These small sources permit application not previously practicable as in the pituitary fossa (see Figure 27 17) This size is also useful for the urinary bladder (see Figure 27 18) These sources are so small that their insertion is tolerated

The implantation of metastases to neck nodes abdominal nodes and other regions would appear to be best accomplished by the use of flexible nylon threads with subsequent removal The permanent implantation rarely achieves the dosage symmetry possible by use of linear parallel applicators We are firm believers in the combination of surgical and radiation technics Without a supply of radioactive applicators always avail

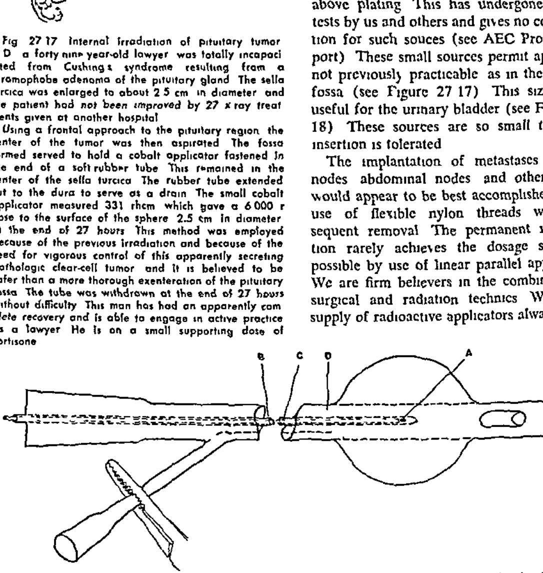


Fig 27 18 Foley urethral catheter with cobalt insert A Radioactive cobalt source a plated cube 1 mm in diameter B Outer *nylon tube* C Inner nylon tube which holds the cobalt in the end D Foley catheter

able for instant use the fullest co ordination is not achieved The possibility of keeping a rapidly decaying source supply on hand has always in the past precluded full availability of such a technic using radon The nylon threads in our opinion are best loaded with cobalt and kept sterile in assorted lengths for immediate use A few cases of 4 year survival of patients with inoperable metastases to cervical neck nodes using this method would appear to justify the attempt

CHAPTER 28

Use of the Radioactive Cobalt Beam for Cancer Therapy

Ivan H Smith
and
John G Brown

PHYSICAL ASPECTS

In 1935 Fermi and others demonstrated gamma emission following the absorption of slow neutrons in metallic cobalt Sampson and others proposed that the long lived portion of the gamma emission belonged to the isotope Co^{60} The further development of the fundamental physics of Co^{60} may be traced by reference to the works of Livingood Risser Nelson and Deutsch

Figure 28 1 depicts the disintegration scheme of this radioactive element It will be seen that Co^{60} emits a 0 308 mev beta ray This is followed by 1 17 and 1 33 mev gamma rays in cascade resulting in the stable disintegration product Ni^{60} The half life of Co^{60} is still somewhat uncertain The accepted half life has been 5 3 years but a recent determination by Lockett and Thomas suggests a value closer to 5 0 years very short indeed as compared to radium Figure 28 2 is a decay curve based on the 5 3 year half life The dose rate from Co^{60} decreases to 98 9 per cent of its initial value in one month The dis

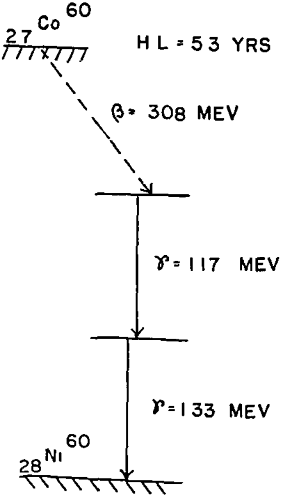


Fig 28 1 Disintegration scheme of the isotope Co^{60}

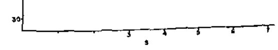


Fig 28 2 Decay curve for Co^{60}

integration constant for a half life of 5 3 years is 0 131 per year=1 09×10 ² per month

Mayneord (1950) has shown that the dose rate from a 1 mc point source of unfiltered Co^{60} is 13 5 r/hour at 1 cm This compares with 8 3 r/hour at 1 cm from a 1 mg radium point source filtered by 0 5 mm platinum Under these conditions 1 mc of Co^{60} produces the same dose rate as 1 63 mg of radium

Co^{60} can be produced by bombarding cobalt metal with deuterons from a cyclotron but it is more conveniently produced in larger quantities by placing the natural metal in the large neutron flux available in an atomic pile

The essential requirements of a radioactive source for teletherapy purposes are that the source have a long half life be pure preferably have a homogeneous high energy gamma emission and have a very high radio active concentration (specific activity i e curies per gram) The latter requirement is important since the shape of the isodose curves depends on the physical size of the source In general the larger the physical dimensions of the source the greater is the radiation penumbra Still another factor to be considered in designing teletherapy units is the increase in percentage depth dose with increasing treat ment distance Consequently it is desirable to have a source that can be used at a large distance will produce an economical dose rate but at the same time be of such a size as to permit good beam definition A further re quirement is that the protection for such a source must not be such as to make the apparatus cumbersome in treating difficult head and neck areas

With the high neutron flux available in the atomic pile at Chalk River Canada it was possible to produce highly concentrated radio active Co^{60} sources that met the above require ments In this pile and now in others thin cobalt discs or small pellets of millimeter dimensions are irradiated With these wafers or pellets it is possible to obtain 1 000-curie cylindrical sources measuring 2 5×1 cm and even smaller with an output of 20 r/min at 100 cm distance

Among the units that have been designed for telecurie therapy are those of Johns (1952) Grimmett and Green The units designed by Johns and Grimmett utilize fixed cones while that of Green is fitted with an adjustable diaphragm Figure 28 3 illustrates the last unit and Figure 28 4 is a simplified cross section diagram of the head and dia phragm system This unit is turned on and off by means of a mercury shutter Detailed description of the design of each unit is con tained in the references

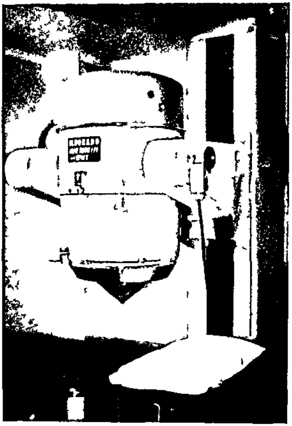


Fig 28 3 A Co^{60} beam therapy unit

A Co^{60} teletherapy unit may be compared to a 2 or 3 mev x ray generator since under comparable conditions it produces similar isodose distributions The Co^{60} unit has no electrical generator and requires a minimum of servicing The output of a 1 000 curie Co^{60} unit is less than present commercial super voltage units but it is not affected by electrical fluctuations A disadvantage of the Co^{60} is the relatively short half life of the source which will have to be reactivated every 3 or 5 years according to individual requirements In addition cobalt teletherapy sources emit radiation continuously and consequently re quire more elaborate built in protection

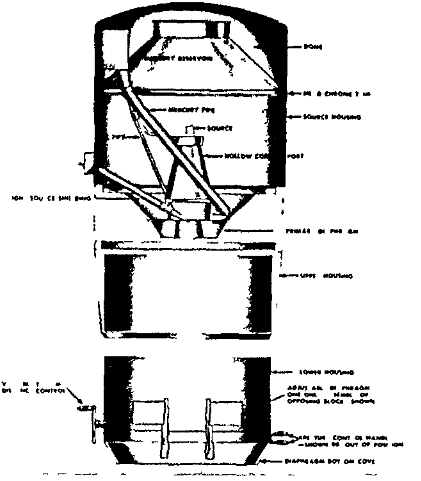


Fig 28-4 Exploded view of the head and diaphragm system of a Co^{60} unit (From Green and Errington [10] courtesy Journal Canadian Association of Radiologists)

ABSORPTION AND INTEGRAL DOSE IN TISSUES

For clinical purposes Co^{60} may be considered as a source of 1 25 mev monochromatic gamma radiation (the beta rays are filtered out) At this energy the absorption coefficients in various tissues are listed in Table 28 1 These values show that absorption in bone is less than that for 250 kv x rays (Spiers) The lower absorption in bone with Co^{60} gamma rays will result in less distortion of ideal isodose distributions when the beam of radiation passes through a hetero

TABLE 28 1 —Absorption in Tissues

Tissue	*Cobalt 60 irradiation Wavelength 0 01 Ångstrom*		*250 kv Irradiation Wavelength 0 10 Ångstrom*	
	Linear absorption coefficient (per cm)	*Energy absorption (ergs per r)*	*Linear absorption coefficient (per cm)*	*Energy absorption (ergs per r)*
Muscle	0 064	93 9	0 160	93 8
Fat	0 060	88 8	0 150	83 6
Bone	0 105	155 0	0 292	245 0

geneous medium of bone and soft tissues From Table 28 1 it is also evident that the energy absorption in ergs per roentgen is less with Co^{60} radiation than with 250-kv x rays This is an advantage when bone is unavoidably in the path of the radiation beam

Integral dose is a measure of the amount of energy absorbed by a patient when treated with x or gamma radiation A dose of one gram roentgen corresponds to the absorption

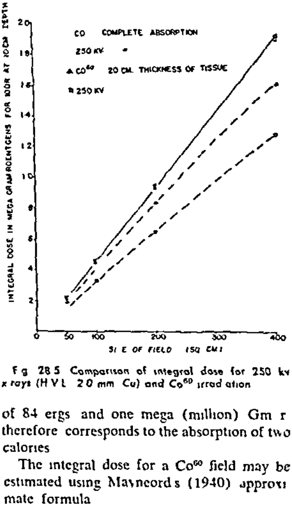


Fig 28 5 Comparison of integral dose for 250 kv x rays (H V L 2 0 mm Cu) and Co^{60} irradiation

of 84 ergs and one mega (million) Gm r therefore corresponds to the absorption of two calories

The integral dose for a Co^{60} field may be estimated using Mayneord s (1940) approximate formula

$$\Sigma = 1\ 44\ D_o\, A\, d_1 \left[1 + 2\ 88\frac{d_1}{f} + 4\ 15\left(\frac{d_1}{f}\right)^2\right]$$

where D_o=given dose A=area of field d_1= depth of 50 per cent isodose curve f=source-to-skin distance

Figure 28 5 shows the variation of integral dose with the size of field namely the larger the field the larger the integral dose From Figure 28 5 it is also evident that for complete absorption of all the incident radiation there is no difference in integral dose between Co^{60} and 250 kv x rays when 100 r is delivered at a depth of 10 cm However in practice the patient has a finite thickness and owing to the greater penetration of Co^{60}, more radiation escapes and results in the lower integral dose indicated in Figure 28 5 Values give order of magnitude only

For single field treatment of a tumor at less than 6 cm depth the integral dose is the same for both Co^{60} radiation and 250 kv radiation For parallel opposing field treatments the integral dose is 10 to 30 per cent less with Co^{60} radiation the difference increasing with increasing separation of fields For 3 field treatment of the larynx (Figure 28 12) the integral dose would be approximately 2 7 megagram roentgens for 5 000 r tumor dose To deliver 5 000 r by 250 kv x rays an integral dose of 2 9 megagram roentgens would be given

In Figure 28 6 the dose in roentgens delivered to the various intervening tissues is shown when 250 kv x ray and Co^{60} 5 field technics are used to deliver 5 000 r to an esophageal tumor With Co^{60} the integral dose is approximately 9 megagram roentgens for 5 000 r tumor dose Using 250 kv x rays the integral dose is 12 5 megagram roentgens for 5 000 r tumor dose These values indicate that integral dose is less with Co^{60} gamma rays for multiple field treatments The difference increases with increasing size of the patient

OUTPUT, BACKSCATTER, H V L, AND DEPTH DOSE DATA

Compared with lower energy radiation Co^{60} gamma rays have the advantage of being more penetrating Another advantage is the build up of ionization below the skin surface producing the maximum dose at a depth of 5 mm rather than on the skin surface as in conventional lower kilovoltage x ray apparatus This build up of ionization is due to absorption taking place by means of forward scattering Johns (1952) has measured this build up of ionization for both small and large fields and Figure 28 7 illustrates results of measurements with a very thin walled ionization chamber Thus skin areas treated with open ended cones will receive 30 to 60 per

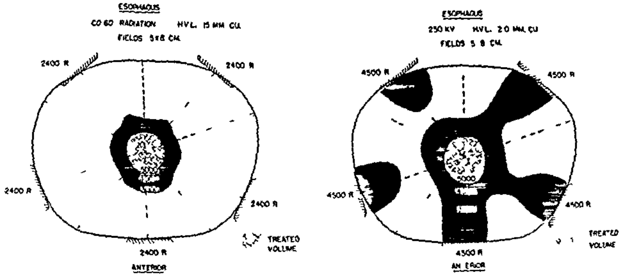


Fig 28 6 (Left) Dose distribution for a 5 field treatment of esophageal cancer with Co^{60} irradiation (*Right*) Dose distribution for a 5 field treatment of esophageal cancer with 250 kv x rays

TABLE 28 2 —OUTPUT OF A 1000 CURIE COBALT BEAM UNIT
(Source skin distance 100 cm)
(Diaphragm skin distance 21 cm)

Field size (cm)	*Column 1* *Air dose rate (r/min)*	*Column 2* *Dose rate with backscatter (r/min)*	*Column 3* *Per cent backscatter*
5×5	20 0	20 2	1 0
10×10	20 9	21 6	3 3
20×20	21 5	22 5	4 6
5×10	20 3	20 7	2 0

(*Courtesy* Radiology Laboratory National Research Council Canada)

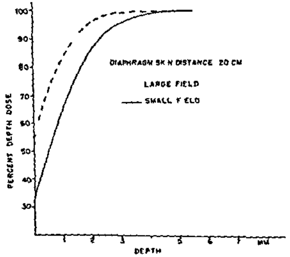
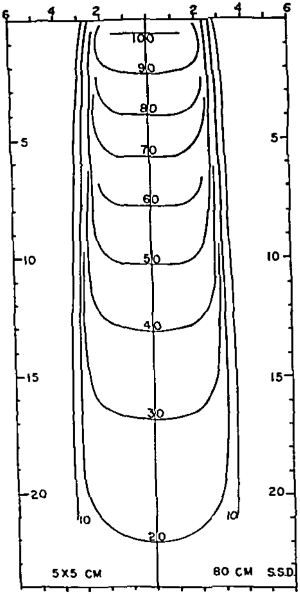


Fig 28 7 Build up of ionization below skin surface with Co^{60} irradiation

cent of the dose delivered at 5 mm depth The build up of ionization is influenced by electrons produced in the diaphragming system the air, and other intervening materials between source and skin surface Johns has shown that the optimum diaphragm to-skin distance is 20 cm or more The build up of ionization is similar to that obtained by Miller and Wilson with 2 mev x ray apparatus

To measure the output of the Co^{60} teletherapy unit it is necessary that the ionization chamber have a wall thickness of 3 to 4 *mm* to produce electronic equilibrium A thin walled Victoreen 25 r chamber with a 3 mm lucite cap is suitable for measuring the output of these teletherapy units Table 28 2 gives the values of output measured both in air and



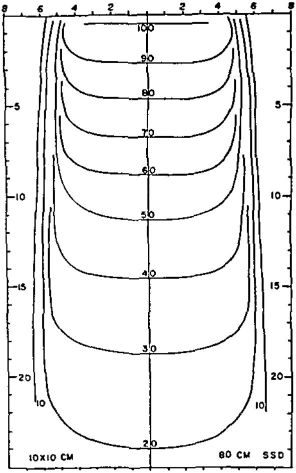


Fig. 28.8. (*Left*) Isodose distribution for a 5 × 5 cm field Co^{60} irradiation. H.V.L. 15 mm Cu. S.S.D. 80 cm. (*Right*) Isodose distribution for a 10 × 10 cm field Co^{60} irradiation. H.V.L. 15 mm Cu. S.S.D. 80 cm.

with the Victoreen chamber half in and half out of a phantom. The increase in values in Column 2 is due to backscatter. For small fields the backscatter is 1 to 2 per cent while for large fields it is of the order of 5 per cent. The variation of air-dose rate with field size is due to scattering from the diaphragm.

The half value layer of Co^{60} radiation is 11 mm. lead or 15 mm. copper.

Depth dose tables for Co^{60} teletherapy units have been published by Dixon (1952), Johns (1952) and Fedoruk (1953). In Table 28.3 are depth dose values for source-to-skin distances of 80 and 100 cm. Values in Table 28.3, when compared with those obtained for lower kilovoltage x rays, indicate that the percentage increase in depth dose is greater for small fields than large fields. Comparison with supervoltage x rays indicates an equivalence to 2 or 3 mev. Two isodose distributions are shown in Figure 28.8 for a diaphragm to skin distance of 24 cm. and an S.S.D. of 80 cm. The width of penumbra for these fields may be calculated using the formula $d=2a(L/l-1)$ where d is the penumbra, $2a$ the diameter of the source, L is the source-to-skin distance and l is source to diaphragm distance. For distributions in Figure 28.8 the calculated penumbra is 1.0 cm. The effect of this penumbra is to eliminate the sharp discontinuity at the edge of the field that is obtained with lower energy x rays.

For elongated fields where ratio of sides is less than 2.5:1, it is possible to use the depth

TABLE 28 3.—DEPTH DOSE FOR COBALT 60 RADIATION

Depth (cm)	SSD 60						S.S.D 80						SSD 100					
	Area in Square Centimeters						*Area in Square Centimeters*						*Area in Square Centimeters*					
	0	20	50	100	200	400	0	20	50	100	200	400	0	20	50	100	200	400
0.5	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1	95.0	96.7	97.1	97.8	97.9	98.1	95.4	97.0	97.7	98.2	98.4	98.5	95.9	97.2	97.9	98.6	98.8	98.8
2	86.0	90.1	91.2	92.2	92.6	93.0	87.1	91.0	92.5	93.4	93.7	94.0	87.9	91.7	93.0	94.0	94.5	94.6
3	77.9	83.7	85.4	86.6	87.4	88.0	79.5	85.3	87.2	88.4	89.0	89.6	80.7	86.3	88.1	89.4	90.1	90.5
4	70.7	77.6	79.7	81.2	82.3	83.2	72.7	79.6	82.0	83.4	84.4	85.2	73.8	81.0	83.2	84.8	85.7	86.4
5	64.2	71.7	74.2	75.9	77.3	78.4	66.5	74.1	76.9	78.5	79.9	80.8	67.8	75.7	78.4	80.2	81.3	82.3
6	58.3	66.1	68.9	70.7	72.4	73.7	60.8	68.9	71.8	73.7	75.2	76.4	62.3	70.6	73.6	75.6	76.9	78.2
7	53.0	60.8	63.7	65.7	67.6	69.2	55.6	63.8	66.8	68.9	70.7	72.1	57.3	65.7	68.8	71.0	72.5	74.1
8	48.2	55.8	58.8	60.9	63.0	65.0	50.9	58.9	62.1	64.2	66.3	68.0	52.7	61.0	64.2	66.5	68.3	70.1
9	43.9	51.2	54.2	56.4	58.6	60.9	46.6	54.3	57.5	59.8	62.1	64.1	48.5	56.5	59.7	62.1	64.2	66.2
10	39.9	46.9	49.9	52.2	54.5	57.1	42.7	50.1	53.3	55.7	58.1	60.3	44.7	52.3	55.5	57.9	60.3	62.5
11	36.3	43.0	46.0	48.3	50.7	53.4	39.2	46.2	49.4	51.8	54.3	56.7	41.2	48.4	51.6	54.0	56.6	58.8
12	33.1	39.4	42.4	44.7	47.2	50.0	35.9	42.6	45.8	48.2	50.8	53.3	38.0	44.8	48.0	50.4	53.1	55.4
13	30.2	36.1	39.1	41.4	44.0	47.0	32.9	39.3	42.4	44.9	47.6	50.1	35.0	41.5	44.6	47.1	49.8	52.2
14	27.5	33.1	36.0	38.3	41.0	44.0	30.2	36.3	39.3	41.8	44.5	47.1	32.2	38.5	41.5	44.0	46.7	49.2
15	25.1	30.4	33.2	35.5	38.2	41.2	27.7	33.5	36.4	38.9	41.8	44.3	29.6	35.7	38.6	41.1	43.8	46.4
16	22.9	27.9	30.6	32.9	35.6	38.6	25.4	31.0	33.8	36.2	39.0	41.7	27.2	33.1	35.9	38.4	41.1	43.7
17	20.9	25.7	28.2	30.5	33.2	36.2	23.3	28.7	31.3	33.8	36.5	39.2	25.0	30.7	33.4	35.9	38.6	41.2
18	19.1	23.7	26.0	28.3	31.0	34.1	21.4	26.5	29.0	31.4	34.2	36.9	23.0	28.5	31.1	33.6	36.3	38.8
19	17.4	21.8	24.0	26.2	28.9	32.0	19.6	24.5	27.0	29.3	32.0	34.7	21.2	26.4	29.0	31.4	34.1	36.6
20	15.9	20.0	22.1	24.2	27.0	30.0	18.0	22.6	25.0	27.3	30.0	32.7	19.5	24.4	27.0	29.2	32.0	34.5

(From Johns et al [19] courtesy British Journal of Radiology)

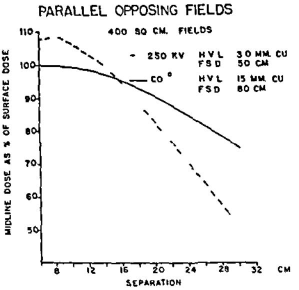


Fig 28 9 Comparison of mid line dose obtained with 250 kv x rays and Co^{60} irradiation for parallel opposing feld techn c (per cent of dose at 5 mm depth for Co^{60} irradiation)

dose values in Table 28 3 for the same area provided an error of 2 per cent is permissible The depth dose values at the larger depths are affected more than those at depths less than 10 cm For example the depth dose values obtained with a 15×6 cm field will be only 0 5 per cent less at depths up to 10 cm and 1 3 per cent less at 20 cm depth than that for a square field of 90 sq cm area For fields with elongation factors up to 4 the maximum correction is −4 per cent at the larger depths

When treatment fields strike the surface obliquely the effect on central axis depth dose values is negligible However the isodose curves are distorted so that instead of being flat they are inclined to the central axis at an angle equal to half of the incident angle Howarth who investigated this effect with 2 mev x rays found similar results

METHODS OF TREATMENT AND ISODOSE DISTRIBUTIONS

In Figure 28 9 the dose obtained at mid line with Co^{60} parallel opposing fields is compared with that obtained with 250 kv x rays For Co^{60} the values are expressed as a percentage of the maximum dose which occurs at 5 mm depth rather than on the surface It is evident that for small separation of the fields Co^{60} does not produce as large a mid line per centage depth dose but for large separations the Co^{60} beams produce the larger percentage mid line dose In addition the dose on skin surface must be considered and Co^{60} has a distinct advantage as shown by Figure 28 10

Treatments requiring accurate multiple field beam direction are carried out using the plaster shell plus backpointer method of Paterson The method is as follows A plaster shell is fitted to the body area to be treated tumor localization radiographs are taken with patient wearing the shell to which lead identification markers have been attached an outline of shell at the level of the tumor is made using

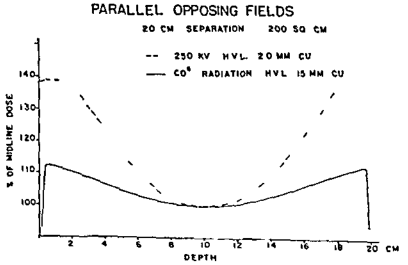


Fig 28 10 Compa ison of dose in a 20 cm th ckness of t ssue treated with 250 kv x ray and Co^{60} irrad at on

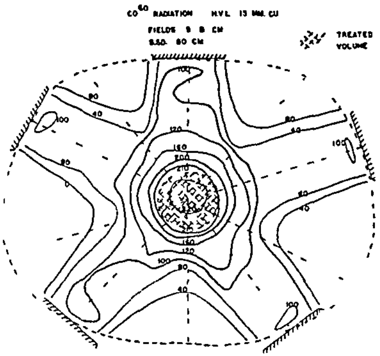


Fig 28 11 Isodose distribution for a 5 field Co^{60} treatment of esophageal cancer

a flexible lead wire, the position of tumor determined from radiographs is marked on the cross section diagram and the treatment is planned with the aid of isodose curves The number of fields is determined by the tumor-to-healthy tissue dose ratio required These fields are placed to give as homogeneous an irradiation of the tumor volume as possible When entrance and exit points of the fields have been determined on the diagram they are marked on the plaster shell Holes are drilled in the shell at these points so that the pointed plastic treatment cone and back pointer can be fitted into them during treatment Figure 28 13 is an illustration of a patient being treated by this method and Figure 28 11 is an isodose distribution for an esophagus treated in this way The tumor dose of 220 per cent may be compared with 110 per cent obtainable with a 5 field 250 kv x ray treatment Figure 28 12 is the isodose distribution obtained using a 3 field plaster shell plus backpointer technic in treating the larynx

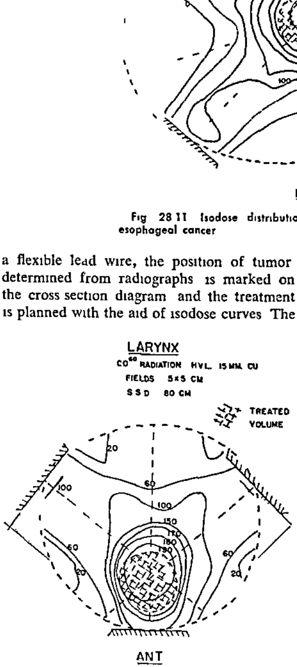


Fig 28 12 Isodose distribution for a 3 field Co^{60} treatment of laryngeal cancer

Where plaster casts are not feasible as in pelvic lesions another method of beam direction is the Manchester pin and arc In Figure 28 14 a patient is shown under treatment using this instrument Figure 28 15 is a schematic diagram of the pin and arc The arc is designed so that its center moves along

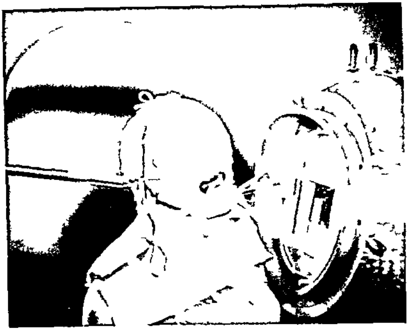


Fig 28 13 Patient being treated with the aid of backpointer

Fig 28 14 Patient being treated with aid of pin and arc

the beam axis The vertical depth a of the tumor below the point P marked on the skin surface is set on the pin The angle C at which beam is required to enter patient is set on the arc A The distance b from center of tumor to beam entrance point is set on the scale D The cobalt machine is then placed so that the pin is vertical and the tip of the pin is resting on the skin mark P In this position the central axis of radiation beam passes through the center of the tumor

Watson has outlined a method of using the pin and arc for setting up patients who are rotated during treatment With Co^{60} tele therapy units it is possible to obtain better tumor-to-skin dose ratios than are shown in Figures 28 11 and 28 12 Instead of the 2 2 1 ratio obtained with the 5 field treatment of esophagus in Figure 28 11 one could ob tain a 5 1 ratio using rotation Dose distribu tions obtained with 2 mev x rays during horizontal rotation of the patient have been

published by Steed Hare has also published dose distributions for rotation technics using a 2 mev x ray generator

PROTECTION AND INSTALLATION

The protection required for Co^{60} multicurie teletherapy units can be divided into two parts namely protection against direct beam radiation and protection against scattered radiation The amount of protection required can be determined from the absorption measurements of Dixon [6]

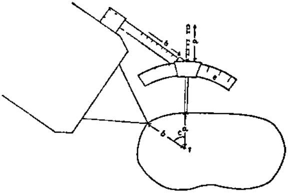


Fig 28 15 Schematic diagram of pin and arc method of treatment

The amount of scattered radiation inside a treatment room for a dose rate of 22 r/min at the treatment distance and 20 × 20 cm field is shown in Figure 28 16 Factors that affect the amount of scattered radiation are dose rate size of field and size of scattering medium In general doubling dose rate doubles the amount of scattered radiation increasing field size increases scattered radiation and increasing size of scattering medium decreases the amount of scattered radiation

The advantage of the maze entrance to the treatment room is the much smaller quantity of lead required for the treatment room door The walls of the room in Figure 28 16 are 12 inches of solid concrete

CLINICAL ASPECTS

Clinical comments and observations for this chapter are based on the 1 000 curie unit of The Ontario Cancer Foundation London Clinic in operation since October 27 1951 Six hundred and fifty three patients were treated during the first 18 months Selection of patients although desirable has been badly stilted because of demands for palliative assistance to many advanced problems, never theless an attempt has been made precisely to carry the dose higher and higher fully utilizing the physical advantages offered by Co^{60} in an effort to gather factual data on this new form of external irradiation We view our work still as clinical research and any deductions presented should be interpreted as

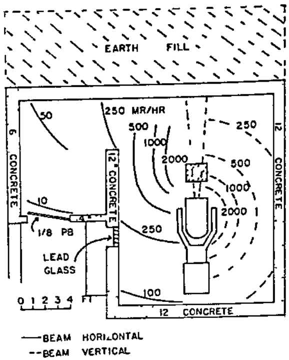


Fig 28 16 A Co^{60} beam unit treatment room showing the amount of scattered radiation inside room for a 22 r/min dose rate at treatment distance

an interim report produced 18 months after installation of the unit on patients treated during the first 14 months

Physical and clinical observations previously made on conventional x ray radium bomb and particularly on supervoltage x ray paved a basic line from which to start All have in common along with Co^{60} ionization of cells as the fundamental reason for the biologic phenomena induced yet Co^{60} has a potential approximating 3 mev and two single wave lengths in contrast to the broad heterogeneous spectrum of x ray equipment Could such a monochromatic beam the aspiration of radiotherapist and physicist for some fifty years have any biologic significance perhaps even some biologic specificity? The answer might well be No were we to subtract such

physical side effects presented previously as lower coefficient of tissue absorption decrease of backscatter and lower integral dosage reasoning in terms of total ionization alone This we have been prepared to do nevertheless it must be admitted that the complexity of the human body unlike the relative simplicity of the ionization chamber makes man a crude indicator of potential biologic differences in ionizing wavelengths The biology laboratory may yet have to settle this question

Co^{60} teletherapy and supervoltage x rays have expanded the effectiveness of radiotherapy and trends predicted are along the following lines

1 New postoperative fields

2 A widened field of palliative usefulness in sites ofttimes neglected

3 A legitimate encroachment on conventional therapy

4 A continued determined effort to establish a cure rate in certain inoperable not advanced deep-seated cancers as in the lung esophagus rectum and bladder

Fig 28 17 Patient being treated for bronchogenic carcinoma (From Smith [39] courtesy Journal Canadian Association of Radiologists)

The physical advantages of Co^{60} over conventional x ray therapy paralleling supervoltage of the two to three million range have been reviewed

There is sufficient evidence to give us the impression supported increasingly as time goes on that the definite band of physical advantages has its clinical parallel in a band forced to be a little broader because of associated biochemistry pathology and indeed psychology in general however the clinical band of improvement parallels the physical A higher dose both locally and systemically is tolerated in a shorter time but this is a very broad statement and how valid it is for specific sites will only be learned from an appraisal of results in numbers statistically valuable

Speaking categorically and in a broad way

DOSAGE EXPERIENCES FOR LARYNGEAL CARCINOMA

A 5 500 r T D (tumor dose) beam directed delivered in 3 weeks in the average case achieves a maximal mucosal reaction compatible with safety and is the basic maximum figure used within this study period Ten patients are available for study All had intrinsic carcinoma regarded mostly as late Stage 2 Three patients showed early recurrences Seven patients have cleared clinically and are free of cancer 5 to 16 months

Figure 28 12 indicates an isodose study of the typical 3 portal larynx technic Plaster collar with backpointer technic was used throughout (Figure 28 13) Where the lesion

is confined to one side, the single field technic is finding its place

In consideration of our own experience with conventional therapy it is our impression that the larynx group supports the idea that, with Co^{60} irradiation it is possible to deliver a greater dose in a shorter time Furthermore a legitimate encroachment on conventional therapy appears to be justified and this trend so predicted Tumor dosage and time are listed below Time has permitted no observations on delayed necrosis nor delayed recurrences

Carcinoma of larynx (total 10 patients)

The clinically well group
(7 patients out of 10 total)

1 Case	T D 5 500 r	3 weeks
2 Cases	T D 5 550 r	3 5 weeks
1 Case	T D 5 200 r	4 weeks
1 Case	T D 6 000 r	4 weeks
1 Case	T D 6 500 r	4 weeks
1 Case	T D 5 500 r	5 weeks

The recurrent group
(3 patients out of 10 total)

1 Case	T D 4 500 r	3 weeks
1 Case	T D 5 200 r	4 weeks
1 Case	T D 5 400 r	5 weeks

DOSAGE EXPERIENCES IN ORAL CARCINOMA

Fourteen patients are suitable for dosage study The tremendous variability of radio sensitivity mitigates the value of observations made on any small group This is most apparent in 2 patients staged as 3 and 4 of carcinoma of the tongue with bulky fixed primary lesions and 1 with metastases in bilateral cervical nodes one is free of cancer 14 months later, receiving a tumor dose of 6 000 r in 7 weeks, the other, an old man is well 12 months later receiving a tumor dose ranging from 3 000 to 4 000 r in 3 weeks Large parallel opposing fields were used and probably the increased depth dose has revealed its value in the response of one of the two patients with metastatic cancer in lymph nodes

To offset such surprises is the very superficial keratinizing epithelioma covering most of the soft palate which persisted after a tumor dose of 5 600 r in 3 5 weeks

High dose observations (1 patient well) One cancer of the floor of mouth 3 5 cm in diameter, received treatment through parallel opposing fields over 4 weeks to a tumor dose of 7,300 r The skin receiving 6 000 r showed a fibrinous reaction, as did the tumor and oral mucosa There was a minimal mucosal dryness The teeth not removed were firm after 10 months Repair was perfect For the time being T D (tumor dose) of 7 000 to 7 500 r in 4 to 5 weeks is what we term our optimum aim

Low dose observations (4 patients well) One patient with Stage 3 carcinoma of the buccal surface of the cheek on whom we discontinued therapy at a T D of 3 000 r in 2 weeks has been free of cancer for 14

Summary of dosage study in oral carcinoma (total 14 patients)

High dose observations (1 patient well)			
Floor of mouth	Stage 2	T D 7 300 r	4 weeks
Low dose observations (4 patients well)			
Buccal surface cheek	Stage 3	T D 3 000 r	2 weeks
Tongue	Stage 4	T D 3 000 4 000 r	3 weeks
Recurrent tonsil	Stage 2	T D 4 300 r	3 weeks
Tongue	Stage 3	T D 6 000 r	7 weeks
Average dose observations (4 patients well)			
Fauces	Stage 2	T D 5 500 r	3 weeks
Tongue	Stage 3	T D 5 500 r	3 weeks
Hard palate	Stage 3	T D 5 600 r	3 5 Weeks
Soft palate	Stage 3	T D 6 500 r	4 weeks
The recurrent oral group (5 patients out of 14 total)			
Alveolus	Stage 2	T D 5 000 r	3 weeks
Anterior pillar	Stage 2	T D 5 500 r	3 weeks
Anterior pillar	Stage 3	T D 5 500 r	3 5 weeks
Tongue	Stage 3	T D 6 000 r	4 weeks
Floor of mouth	Stage 3	T D 6 000 r	4 5 weeks

months A patient with Stage 2 recurrent carcinoma of tonsil is well 9 months from a T D of 4 300 r in 3 weeks A patient with Stage 3 carcinoma of tongue is free of cancer 14 months from 6 000 r in 7 weeks One patient with Stage 4 carcinoma of the tongue receiving a tumor dose of 3 000 to 4 000 r in 3 weeks is well 1 year later

DOSAGE EXPERIENCES IN BLADDER CARCINOMA

Nine cases are available for study Owing to massive tumors with extravesical spread 4 received large parallel opposing pelvic fields with tumor dosage of 2 500 to 4 000 r in 3 to 3 5 weeks Two of these were palliatively relieved of symptoms while 2 received no benefit The remaining 5 patients by pin and arc technic received 5 000 r bladder dosage to volumes averaging 10 cm in from 3 to 3 5 weeks Slight to moderate yet tolerable early reactions followed Four have remained practically symptom free and 3 of them cystoscopically clear for 4 to 10 months In each instance the tumor was confined to the bladder but beyond desiccation or excision control and either partial or total cystectomy had been recommended It is considered inadvisable to shorten the over all time for a tumor dose of 5 000 r in fact to protract at the same or slightly reduced dosage rate into the fourth or fifth week seems to have merit in instances particularly of bulky residual growths One ulcero infiltrating Grade I keratinizing cancer showed no response

The satisfactory observations in this group of uncontrolled bladder cancer of course mean much to date for the particular patient It is encouraging to say the least and wishful thinking would have it hold all it really means with so short a follow up is that a safe workable dosage has been established from which to carry on It has been learned that if the tumor is bulky the devitalized tissue may require frequent bladder irrigations

DOSAGE EXPERIENCES IN BRONCHOGENIC CARCINOMA

This is the group in which we had hoped for some moderately early cases Most have been inoperable and proved so by thoracotomy The simple radiotherapeutic point which explains our position is that if we estimate the volume for treatment to be 8 cm and under an attempt at curative dose is given being in the range of 5 000 r to 6 000 r to this volume in 3 to 4 weeks If the treatment area is beyond 8 cm as have been 70 per cent of our cases the danger involved in approaching a curative dose is too hazardous and at the outset palliation is accepted

Palliation consists of 3 000 to 3 500 r central dosage in 3 weeks using parallel opposing fields in size even up to hemithorax This means an average of 2 500 to 3 000 r to the skin with little systemic reaction as a rule and no skin effect

Four field pin and arc is used in an intermediate group where size close to the 8 cm figure but perhaps a little larger warrants an attempt to deliver a low cure dose per chance the tumor exhibits unusual sensitivity

The 5 portal plaster jacket backpointer method is used in the high dose group (Figure 28 17) Rotation here presents its cardinal virtues and will be selectively used in lieu of beam direction

The immediate response in lung cancer has been in the main most gratifying and often dramatic Radiographic improvement as a rule has not paralleled clinical regression In the high dose group esophagitis has contributed its anguish indeed one case at autopsy

Carcinoma of bladder (total 10 patients)

1 Patient	Excluded	(completed 5 of 15 treatments)		
2 Patients	T D 4 000 r	3 weeks	Large fields	No benefit
1 Patient	T D 2 500 r	3 weeks	Large fields	Fair palliation
1 Patient	T D 4 000 r	3 weeks	Large fields	Fair palliation
5 Patients	T D 5 000 r	3 3 5 weeks	4 fields pin and arc 4 of these relatively symptom free 3 cystoscopically clear 4 to 8 months	

showed esophageal ulceration

Attempting to appraise the effectiveness of therapy on a group the first of whom was treated 18 months ago the last only 4 months ago, on the surface appears to be stupid and fair neither to author nor reader To have no answer at all is more stupid To have the right answer to what is being accomplished by Co^{60} at so early a date is impossible Our figures are presented for what they are worth realizing they will alter month by month until stabilized by the conventional 5 year period Of the 84 patients with bronchogenic cancer 15 are excluded mainly because treatments were discontinued within a few days or the patient died within a few weeks from cerebral or spinal metastases or the treated cancer was metastatic rather than primary in the lung Of the remaining 69 19 received no benefit whereas 50 or 27 5 per cent have proved worthwhile—some of short duration some dramatic Twenty three of those receiving palliative benefit are dead 27 are alive 4 to 16 months

DOSAGE EXPERIENCES IN CARCINOMA OF THE RECTUM

Bulky rectal carcinoma of the ampulla inoperable because of extent or age or recurrent rectal carcinoma within the pelvis or perineum is worthy of palliative therapy Thirty three such rectal patients mostly advanced or recurrent were available for study up to December 31 1952 Eight were not benefited 1 perforated 25 or 75 per cent were appreciably helped and therapy in this group was fully justified Dosage observation and response in this rectal group have prompted the recommendation of postoperative cobalt Initially selection will probably be determined by the presence of local extension metastasis to lymph nodes or degree of anaplasia

It is apparent from our dosage experience in this group of patients with cancers of marked radioresistance that a tumor dose of 5 000 r in 3 weeks should be the aim if treatment volume is limited to 8 to 10 cm Some patients tolerated this dosage without incident an equal number experienced cystitis and proctitis of a severity sufficient to create an annoying anxiety In the group of patients with recurrent cancer in the perineum a single field to 15 × 15 cm has been used and daily dosage given Posterior urethritis is annoying as the given dosage approximates 5 000 r In the group with recurrence within the pelvis through and through palliative fields to a central tumor dose of 3 000 to 4 000 r in 3 to 4 weeks has been our objective Where the tumor is primary and within a spherical field of 8 to 10 cm a 3 to 4 portal pin and arc radical technic is used Two such patients went beyond the year without symptoms but both have subsequently shown early local recurrences

DOSAGE EXPERIENCES IN CARCINOMA OF THE STOMACH

Bulky carcinomas of the stomach without obstruction in the frail or elderly individual deemed inoperable have proved a fruitful and interesting study Pain and slow bleeding have cleared appetite has been restored and ability to consume bigger meals has been noticed with sufficient consistency to carry on an energetic dosage study in this group Radiographic improvement is the rule as is radiographic recurrence followed later by a return of symptoms Two of our patients have gone beyond the year most are in trouble within 4 to 6 months Several have had no apparent radiation sickness Two have had delayed (6 months) perforations Up to December 31 1952 of 20 patients with gastric cancer nothing was achieved in 10 palliation was worthwhile in 10 although 4 of these are dead and the remaining 6 are alive 5 to 16 months

Central tumor dosage has been achieved by parallel opposing fields varying in size from 15 × 15 cm to 20 × 20 cm 3 000 to 3 500 r T D in 3 to 3 5 weeks is readily accomplished Rotation therapy and the possibility of synergistic chemotherapy should hold additional promise

A hollow viscus may be endowed with some natural reparative ability but its restorative power as the tumor melts away is woefully lacking and is the constant mental check on our desire to carry the dose to a lethal point Be this as it may the renewal of a patient s interest in the T bone steak has its quiet compensations

Protection and Treatment of Radiation Reactions

CHAPTER 29

Protection in Radiation Therapy*

Eugene T. Leddy

HISTORIC DEVELOPMENT

The earliest workers in roentgenology had no reason to anticipate any injurious effects from roentgen rays and made little attempt at protection [25, 28]. However, within a period of ninety days after the publication of Roentgen's *Preliminary Communication*, suspicion was aroused that roentgen rays or something else evolved in the production of such rays might have some ill effect on living tissues [5, 8].

It was first thought that protection was necessary only against the roentgen rays emanating directly from the target, and the tubes were surrounded by metallic plates or encased in wooden boxes painted with many coats of white lead. The actual time at which lead glass first was used as a protective device is uncertain, but it was used by some of the earliest investigators.

Roentgen appreciated the presence of scattered radiation but attention was first drawn to its possible danger about 1903 when a multitude of devices such as hoods, aprons, jackets, gloves, and goggles which could be worn by the roentgenologist came into use. However, because their bulkiness restricted the actions of the roentgenologist, protective devices were built into the roentgen ray apparatus.

The endeavor to establish the maximal dose of roentgen rays that could be tolerated continuously and safely by the human body had been undertaken as early as 1902 by Rollins. He said that if a photographic plate is not fogged in 7 minutes the radiation is not of harmful intensity for nearly continuous exposure. Kassabian (1910) pointed out the necessity of measuring the total dosage and reviewed the efforts that had been made up to that time.

The first organized step toward protection against injury with the roentgen rays was made in June, 1915, by the British Roentgen Society [46].

Attention was focused on the need for protection in a most unpleasant and vivid manner as a result of a succession of deaths from aplastic anemia. These deaths, which occurred about 1920 or 1921, may have been the result of the excessive exposures taken by roentgenologists in hospital work during World War I. The resulting publicity stimulated action and, as a result, workable safety measures were established.

France appears to have been one of the first countries to set up safety regulations, and this was accomplished shortly after World War I. The few original regulations, while they had a certain degree of legal standing, gradually were neglected.

In Germany, the Standardization Committee of the Deutsche Roentgen Gesellschaft first met in 1917 and under the supervision of the Reichsanstalt established a standardization of roentgenologic apparatus.

The first permanent Roentgen Ray Protection Committee was formed by the American Roentgen Ray Society in September, 1920, and rules governing radiation protection were formulated at their annual meeting in September, 1922. In 1921 several medical and

* Because of the rapid advance in the field of radiation protection since Doctor Leddy's illness and death, this chapter has been subject to major modifications by the editors in order to present the latest recommended protection data. It is obviously impossible to present all factors pertaining to protection from ionizing radiations; hence certain pertinent material has been selected to show the scope and method of handling this increasingly vital problem.

radiologic groups in England formed a co operative committee that published the first general set of protective recommendations [60] In substance these two sets of recommendations were much the same and the fundamentals of protection put forth in the reports of these two original committees have remained essentially unaltered The legal status of safety recommendations was brought up at the outset and it is important to note taken from them almost verbatim The Congress subsequently adopted these tentative recommendations and appointed an International Committee on X Ray and Radium Protection The Fourth International Congress of Radiology, which met in Zurich in 1934 made no essential modifications in the previous recommendations but made tentative suggestions for protection against injury with super voltage roentgen rays and large quantities of

Fig 29 1 Failla thermionic radon measuring apparatus showing measuring unit in fore ground and remote control recording meters 20 feet away

that in no country do such recommendations have a strictly legal recognition

Protection against injury with radium and roentgen rays was discussed at the First International Congress of Radiology London in 1925 but no official action was taken At the Second Congress held at Stockholm in 1928 representatives of three of the countries that had protective recommendations agreed informally on a set of proposals for international adoption which were based on the early British recommendations and were in fact radium and considered in greater detail several of the protective recommendations concerning the roentgen rays The influence of these protective recommendations has become very evident [64] Manufacturers of roentgenologic apparatus both in this country and abroad now emphasize in an impressive way the protective features of their machines

In addition to the International Protection Committee most countries now have their own permanent committees to deal with the specialized problems that arise continually In

England the National Physical Laboratory stands ready to test and certify protective devices Although this service is optional it has the full support of manufacturers roent Committee on X Ray and Radium Protection whose purpose is to serve as a liaison between the radiologic profession the U S Bureau of Standards and the International Committee

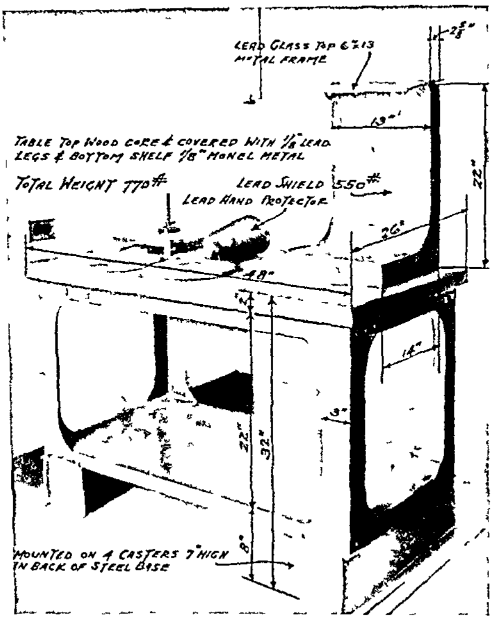


Fig 29 2 Radium assembly table Mobile unit designed to protect the technician while handling the radium and assembling the various applicators

genologists and hospitals The U S Bureau of Standards does not foster any general out side inspection nor have funds ever been authorized for this purpose It does however test and certify protective materials and con curs in the recommendations of the Safety Committee appointed by radiologic groups [10] In this country there is also an Advisory This group composed of representatives of the various radiologic and medical societies and manufacturers of roentgenologic equip ment has prepared a set of detailed recom mendations that are published at intervals in the journals of both the American Roentgen Ray *Society* and the Radiological Society of North America

The National Committee on Radiation Protection, whose function is the investigation of protection against radiation operates under the sponsorship of the National Bureau of Standards and with the co operation of the leading radiological organizations It was formed upon the recommendation of the International Commission on Radiological Protection *The following parent organizations comprise the main committee* American College of Radiology American Medical Association American Radium Society American Roentgen Ray Society, National Bureau of Standards National Electrical Manufacturers Association Radiological Society of North America U S Air Force U S Army U S Atomic Energy Commission U S Navy and U S Public Health Service

The recommendations of the National Committee on Radiation Protection are published in a series of handbooks by the National Bureau of Standards of the U S Department of Commerce and are available from the Superintendent of Documents Washington, D C at slight cost The reader is referred to these for detailed recommendations on radiation protection

The International Commission on Radiological Protection which met in Geneva in 1956 adopted practically all of the recommendations of the National Committee on Radiation Protection of the United States These recommendations have not been published at the present writing (1958)

Brown in *American Martyrs to Science Through the Roentgen Rays* has recorded the sufferings that carelessness and the indifferent use of roentgen rays produced in pioneers not conversant with risks of injury from exposure to these rays

The exposure of whole populations to irradiation—the result of fall out from thermonuclear explosions—and the increased use of radioactive materials both in medicine and in industry have demanded painstaking and critical evaluation of protection against radiation with definitive expressions of maximum permissible dose in various types and durations of exposure to ionizing radiations

The *annual natural background dose* from various sources to gonads and bone marrow expressed in millirads per year is given by Laughlin Meurk, Pullman and Sherman [33] as follows

Gonadal from		
	Cosmic rays	26 ± 3
	Earth housing	53 ± 20
	Atmospheric	2 ± 1
	Internal radioactivity	
	Beta and gamma rays	18 ± 3
	Alpha particles	0 5 ± 0 3
Bone marrow from		
	Cosmic rays	26 ± 3
	Earth housing	59 ± 20
	Atmospheric	—
	Internal radioactivity	
	Beta and gamma rays	5 ± 1
	Alpha particles	4 5 ± 2

MAXIMUM PERMISSIBLE RADIATION EXPOSURE

The maximum permissible dose (MPD) for radiation exposure has been steadily lowered through the years as more is learned concerning the occult and cumulative effects of ionizing radiation as may be seen from the following

1 The International Committee on X Ray and Radium Protection (1934) recommended a tolerance dose of 0 2 r/day or 1 0 r/week

2 The U S Advisory Committee on X Ray and Radium Protection endorsed the value of 0 2 r/day in 1931 and the value of 0 1 r/day in 1936

3 *The U S X Ray and Radium* Protection Committee (1941) set 0 1 μg radium deposited in the body as a tolerance limit This limit is considered to correspond to 10^{8} μc of radon/cc of inhaled air or 10^{9} μc of radon/cc in expired air

4 The U S Atomic Energy Projects (1942) adopted 0 1 r/day as the maximum permissible exposure to X and gamma radiation

The permissible dose from external sources of ionizing radiation recommended by the National Committee on Radiation Protection was published in National Bureau of Standards Handbook 59 in 1954 and in an insert to that Handbook dated January 8 1957 [38] Since publication of the handbook the National Committee on Radiation Protection and Measurement has continued the study and review of its recommendations particularly with respect

to genetic effects and the possible shortening of average life expectancy due to radiation exposure of a larger fraction of the population The NCRP agreed upon the formulation of revised recommendations on maximum permissible doses which integrate the national and international views for practical application

The Committee recommends that existing installations should be modified to meet the new recommendations as soon as practicable and that the new MPD limits should be used in the design and planning of future apparatus and installations Because of the impact of these changes and the time required to modify existing equipment and installations it is recommended on the basis of present knowledge that a conversion period of not more than five years be adopted within which time all necessary modifications should be completed

The following is from the Committee s 1957 recommendations [38]

Definitions

For the purposes of this preliminary statement the following tentative definitions are given

Controlled area A defined area in which the occupational exposure of personnel to radiation or to radioactive material is under the supervision of a radiation safety officer (This implies that a controlled area is one that requires control of access occupancy and working conditions for radiation protection purposes)

Workload The output of a radiation machine or a radioactive source integrated over a suitable time and expressed in appropriate units

Occupancy factor The factor by which the workload should be multiplied to correct for the degree or type of occupancy of the area in question

RBE dose RBE stands for relative biological effectiveness An RBE dose is the dose measured in rems (This is discussed in the forthcoming report of the International Commission on Radiological Units and Measurements)

MPD Recommendations for Occupational Conditions (Controlled Areas)

1 *Accumulated dose* The maximum permissible accumulated dose in rems at any age is equal to 5 times the number of years beyond age 18 provided no annual increment exceeds 15 rems Thus the accumulated MPD=5(N 18) rems where N is the age and greater than 18 This applies to all critical organs except the skin for which the value is double

2 *Weekly dose* The previous permissible weekly whole body dose of 0 3 rem and the 13 week dose of 3 rems when the weekly limit is exceeded are still considered to be the weekly MPD with the above restriction for accumulated dose

3 *Emergency dose* An accidental or emergency dose of 25 rems to the whole body occurring only once in the lifetime of the person shall be assumed to have no effect on the radiation tolerance status of that person

4 *Medical dose* Radiation exposures resulting from necessary medical and dental procedures shall be assumed to have no effect on the radiation tolerance status of the person concerned

MPD Recommendations for the Whole Population

5 The maximum permissible dose to the gonads for the population of the United States as a whole from all sources of radiation including medical and other manmade sources and background shall not exceed 14 million rems per million of population over the period from conception up to age 30 and one third that amount in each decade thereafter Averaging should be done for the population group in which cross breeding may be expected

Recommendations for Internal Emitters

6 In controlled areas the permissible radiation levels for internal emitters will conform to the general principles outlined above Where the critical organ is the gonad or the whole body the maximum permissible concentrations of radionuclides in air and water will be one third the values heretofore specified for radiation workers Where single organs other than the gonads are regarded as the critical organ the present maximum permissible concentrations will continue For individuals outside of controlled areas the maximum permissible concentrations should be one tenth of those for occupational exposures [EDITORS NOTE In April 1958 the National Committee on Radiation Protection tentatively eliminated the maximum permissible weekly dose of 0 3 rem while retaining the 13 week dose of 3 0 rems For design purposes an average dose of 5 0 rem/year or 100 mrem/week should be used for controlled areas and 0 5 rem/year or 10 mr/week for outside of controlled areas]

Discussion of Revised Recommendations

7 The MPD for occupational exposure is based on the absence of detectable injury to the individual It remains at its present level of 0 3 rem/week for the whole body Where the dose in any week exceeds this value a dose of 3 rems in 13 weeks may be accepted The 13 week period may start at the beginning of the calendar quarter or the beginning of the week during which the permissible weekly dose was exceeded

8 Some of the rules will be modified by provisions related to an average yearly limitation of occupational exposure to external sources of ion

izing radiation of 5 rems to the blood forming organs gonads and lens of the eyes and of 10 rems to the skin The use of 5 rems in the statement of the revised rules is for the purpose of design and administration The critical limitation will be that defined for the total accumulated dose in paragraph 1 above

9 If a person s occupational exposure is documented or otherwise known with reasonable certainty he may be permitted to use his reserve exposure in accordance with paragraphs 1 and 2 above In all other cases he shall be assumed to have received his maximum accumulated dose as indicated in paragraph 1 above

10 It is considered that with the current and proposed low levels of occupational exposure it is presently not necessary to make special allowance for medical exposure in conjunction with occupational exposure This consideration may later become important The effects of medical exposures have long been considered by this Committee to be the responsibility of the attending physician it is his responsibility to evaluate medical radiation exposure in relation to the health of the individual

11 In the determination of the population dose in the vicinity of radiation sources proper consid e ation should be given to occupancy factor and to workload The exposure of individuals outside of controlled areas may be integrated over periods up to one year

12 While at the moment it is not feasible to determine the average exposure for the population with any reasonable accuracy the adoption of some figure is necessary for planning purposes For the immediate future it may be assumed that the total integrated RBE dose received for all radiation workers will be small in comparison with the integrated RBE dose of the whole population Furthermore persons outside of controlled areas but exposed to radiation from a controlled area constitute only a small portion of the whole population Therefore if this small portion is assumed to receive yearly an average per capita dose of 0 5 rem the total dose to the whole population from manmade radiations is not likely to exceed 10 million rems per million of population up to age 30 (This assumes a dose of 4 million rems per million of population over this age period from background radiation)

PROTECTION FROM INJURY BY ROENTGEN RAYS

The dangerous biologic effects from roentgen rays necessitate adequate protection not only of the patients but also the physicians and other personnel Since the intensity of radiation decreases by the inverse square law one of the most important protective measures is to insist that all personnel remain as far away as possible from all sources of radiation whether or not there is intervening direct protection

In general one should realize that no protection against roentgen rays can be absolute By the well known equation for intensity after passage through an absorptive medium $I = I\ E - ut$, unless t is infinite I will always have a decreasing and possibly a very small value Actually, after the passage of roentgen rays through several millimeters of lead the value of I becomes negligible One other more important but purely physical consideration of protection should be remembered that the absorptive and protective value of any medium is a function of the wavelength of the radiation against which it protects and because of selective absorption great variations may occur in its absorptive and therefore in its protective value Furthermore the absorption of roentgen rays by any medium is great at a wavelength just below the wavelength of its selective absorption the absorption at a wavelength just above this critical selective value is conversely low

In addition to any selective absorption as the voltage at which roentgen radiation is produced is increased the general absorption by the metal rapidly decreases and there is consequently great variation in the protective value of the material

Protective Materials

The two most important protective elements are lead and barium The values for the wavelength of their K radiations are 0 141 Ångstrom units (Å) or 40 000 volts for barium and 0 330 Å or 80 000 to 90 000 volts for lead Above these values the absorptive values will be much lower than they will be just below these voltages It is therefore necessary, when the equivalent lead value of a protective material is given that the wavelength or voltage at which the material has been tested should be stated

The protective materials most commonly used are sheet lead lead glass lead rubber, and barium plaster

SHEET LEAD

As a protective substance metallic lead is of greatest importance but it is not to be regarded as ideal because of its great weight

Furthermore the metal in thick layers is not flexible and where lead plates are used repeatedly cracks from bending the lead may let roentgen rays through in unwanted quantities Other disadvantages are that lead is difficult to keep clean and it is a good conductor of electricity and picks up static charges

Best practice recommends that sheets of lead be welded and not nailed together as nail holes may permit the leakage of roentgen rays These disadvantages of sheet lead of course do not come into serious consideration when lead is to be used for purposes other than the direct protection of the patient The use of sheet lead near the x ray tube is limited A tube holder lined with sheet lead requires a certain minimal distance between the tube and the holder to prevent a spark from passing over to the lead especially when the voltage is high Furthermore the enclosing of an x ray tube by sheets of metallic lead produces the equivalent of a condenser that may cause the operation of the tube to vary

LEAD GLASS

Lead glass is glass that contains lead salts It normally has a greenish tinge but the most heavily impregnated glass may be green and contain 60 per cent or more of lead The modern variety is even in thick sheets free from flaws and of uniform protective value Most lead glasses have a protective coefficient of 0 20 to 0 29 in order to have the protective equivalent of 3⁄16 inch (0 46 cm) of lead the glass must be about 1 inch (2 5 cm) thick This glass is commonly used for the bowls of tubes or for windows in the control booth for medium voltage x ray

LEAD RUBBER

Lead rubber should be made of a good grade of rubber and should have uniformly distributed throughout it the equivalent of at least 1 mm of lead per centimeter of thickness [62] It is nonconductive flexible easy to keep clean and has a long life unless it is abused Its great disadvantage is its high cost

BARIUM PLASTER

Barium cement or plaster has a great advantage over sheet lead for protection of walls as it is not a conductor of electricity Moreover it is cheaper than lead Various concretes with different percentage compositions of iron lead or barium ores have been introduced Composition walls have been used only occasionally in America except for protection against supervoltage roentgen rays (discussed later) but the usual preference has been for metallic lead

OTHER PROTECTIVE MATERIALS

Various other protective materials of more or less unknown or secret composition have been introduced from time to time These should be regarded with suspicion Usually they are made of lead or barium salts held together by a binder Although their initial cost may be low their period of usefulness is short as they usually crack and crumble after a short time Compounds of lead and plastic materials have not been used extensively in this country, and have been used for insulation rather than for protection

Direct Protection of the Patient

At the Mayo Clinic the fields are outlined in indelible ink on the patient s skin Along the margin of the field one or more strips of lead rubber about 1 cm thick approximately 2 5 cm (1 inch) in width and of a length greater than the treatment field are pasted onto the patient s skin with adhesive tape Over them is laid (outside the field) a sheet of lead rubber By this means the intensity of radiation just outside the field of treatment is reduced to 5 per cent or less and an adjacent field as near as 0 5 cm can be irradiated with perfect safety Since the sheets of lead rubber are of sufficient size to cover the patient s body and a portion of the table in addition the intensity of secondary radiation emerging into the room from the patient and the table is markedly reduced

When a moderate voltage (135 kv) is employed in treatment the portion of the patient s body beyond the field of treatment is covered with lead rubber which has a protective equivalent of at least 3 mm of lead When roentgen rays that are generated at 200 kv are used the radiation is confined by lead cones in addition to the use of *lead rubber* Lead or lead rubber can be adapted to protect the eyes the testes or ovaries or other sensitive

portions of the body, as clinical experience demands [15]

Protection of Technicians

It is well known that those who sustain even the smallest daily doses of x rays may, in time and as a result of cumulation of biologic effect manifest evidences of severe and sometimes fatal injury It is to be recommended that principles of protection should be printed in large type and hung up in each roentgenologic department for attention of the personnel

Some form of a sensitive dosage meter or a Geiger counter may be employed, or the operator may carry on his person a small portable ionization chamber or a piece of photographic film This last mentioned device is very sensitive and a blackening of the film that is just clearly visible corresponds to about 0 01 to 0 02 r

The harmful effect of scattered radiation has been emphasized [16 26] and in a busy roentgenologic department such radiation may be of the greatest danger Fortunately improvements in construction of roentgenologic apparatus and the adoption of specifications that prevent electric shock and injury with roentgen rays have to a great extent reduced the necessity for other devices to protect against secondary radiation However since the output of roentgenologic machines is much greater than it was previously, much thicker protecting walls of lead are necessary

Protection Against Ozone and Nitrogen Fumes

Electric discharges from a roentgenologic apparatus may ionize the air and produce noxious gases thereby playing a role in roentgenologic reactions on the part of the patient In well installed roentgenologic equipment the leads are made corona proof a self protecting x ray tube is used and ionization of the air in the room is reduced to a minimum However a good ventilating system with or without suction fans is to be advised on general principles in any installation of apparatus for the administration of roentgen therapy

RECOMMENDATIONS ON X RAY PROTECTION OF NATIONAL COMMITTEE ON RADIATION PROTECTION

The following excerpts are from the National Bureau of Standards handbook on x ray protection [39]

Definitions

Because the correct interpretation of a statement frequently depends upon the precise meaning given to one or more critical terms the following definitions are given for certain words and phrases as they are here used

Shall denotes that the ensuing recommendation is necessary or essential to meet the currently accepted standards of protection

Should is recommended indicates advisory recommendations that are to be applied when practicable

Aluminum equivalent The thickness of aluminum affording the same attenuation under specified conditions as the material in question

Attenuation The decrease in the dose rate of radiation in passing through a material

Concrete equivalent The thickness of concrete based on a density of 2 35 g/cm^3 (147 lb/ft^3) affording the same attenuation under specified conditions as the material in question

Dose The quantity of radiation in roentgens at a given point measured in air The expression measured in air has a definite meaning in radiology namely that the measurement is made at a given point in the radiation field without the presence of the human body or substitute scattering material

Half value layer (HVL) The thickness of attenuating material necessary to reduce the dose rate of any x ray beam to one half its original value The half value layer shall be the half value layer in the region of the dose rate considered

Lead equivalent The thickness of lead affording the same attenuation under specified conditions as the material in question

Milliroentgen (mr) A submultiple of the roentgen equal to one thousandth (1/1000) of a roentgen

Monitoring Periodic or continuous determination of the dose rate in an occupied area (area monitoring) or of the dose received by a person (personnel monitoring)

Occupancy factor (T) The factor by which the workload should be multiplied to correct for the degree or type of occupancy of the area in question

Occupied area An area that may be occupied by persons or radiation sensitive materials

Protective barrier Barrier of attenuating material used to reduce radiation hazards

Primary protective barrier Barrier sufficient to attenuate the useful beam to the required degree

Secondary protective barrier Barrier sufficient

to attenuate the stray radiation to the required degree

Diagnostic type protective tube housing One that reduces the leakage radiation to at most 1 0 r/hr at a distance of 1 m from the tube target and 1 0 r/min. at any point on the surface of the housing when the tube is operating at its maximum continuous rated current for the maximum rated voltage

Therapeutic type protective tube housing One that reduces the leakage radiation to at most 1 0 r/hr at a distance of 1 m from the tube target and 1 0 r/min at any point on the surface of the housing when the tube is operating at its maximum continuous rated current for the maximum rated voltage

Roentgen (r) The quantity of X or gamma radiation such that the associated corpuscular emission per 0 001293 g of air produces in air ions carrying 1 esu of quantity of electricity of either sign

Use factor (U) The fraction of the workload during which the useful beam is pointed in the direction under consideration

Useful beam That part of the primary radiation that passes through the aperture cone or other collimator

Workload (W) The working activity of a machine measured in milliampere minutes per week

Planning, Surveys, and Inspections

1 The structural shielding requirements of any new installation or an existing one in which changes are contemplated should be discussed with a qualified expert early in the planning stage

(a) The expert should be provided with available data concerning the type use and kilovoltage of the machine to be installed in each room the expected workload the structural details of the building and the type of occupancy of all areas that might be affected by this installation

* * * * *

4 Protection survey

(a) A protection survey should be made by or under the direction of a qualified expert of all new installations requiring structural shielding existing installations not previously surveyed and after every change that might increase the radiation hazard

* * * * *

(c) If safe use of the installation depends upon mechanical restrictions of the orientation of the x ray beam and limitations (voltage current time permanent filter and maximum aperture) in the output of the tube then an inspection shall be made to see that these restrictions are actually imposed

(d) All interlocks shall be tested to make certain that they are operating properly A check shall be made to determine that there are a sufficient number of warning signs properly placed

(e) A preliminary survey shall be made with a suitably sensitive radiation-detecting instrument which may be a Geiger counter an ionization chamber or a scintillation counter Every location shall be tested that is habitually occupied or can be occupied while x rays are being produced.

(f) Every location that shows more than one fifth the maximum permissible dose shall be investigated further with a radiation measuring device that is suitably independent of direction and quality or corrected therefor X ray sensitive films and Geiger or scintillation counters may not be suitable for such measurements The x ray machine should be operating at its maximum rated voltage during these measurements

5 Report of protection survey

(a) The expert shall report his findings in writing to the person or agency requesting the survey and to the person in charge of the installation

(b) Dose rates at critical positions shall be indicated in milliroentgens per hour If at any of the indicated positions the permissible dose is likely to be exceeded in a 40-hr week the time that personnel can safely remain at this position or the maximum permissible workload shall also be specified

Working Conditions

* * * * *

5 Personnel monitoring

(a) Personnel monitoring shall be required for each individual for whom there is any reasonable *possibility of receiving a weekly* dose of x rays exceeding one fourth the maximum permissible dose taking into consideration the use of protective gloves aprons or other radiation limiting devices except that if monitoring over a period of 8 consecutive weeks shows that the dose does not exceed one half the maximum permissible *dose then the routine monitoring* of that individual may be eliminated If the operating conditions are changed a new monitoring test over an 8 week period shall be made

(b) It is recommended that a qualified expert be consulted on the establishment of the monitoring system Permanent records shall be kept of all personnel monitoring results

(c) Monitoring may be done with film badges pocket chambers or pocket dosimeters *Periodic blood counts should not be regarded as a means of radiation monitoring*

6 Health

(a) The person in charge shall be responsible for the protection of employees patients and authorized visitors against radiation injuries and for the execution of health regulations for all employees

(b) A pre-employment physical examination is generally advisable This should include a complete history a description of any re to radiation resulting from pre accident or diagnostic or thera

peutic exposure a family history with special emphasis upon heritable defects, and a careful and complete physical examination This last should include urinalysis chest film and a complete blood count the latter repeated after a month No further blood counts are necessary except when the maximum permissible dose is exceeded

(c) In the case of an exposure in excess of the maximum permissible dose an immediate blood count should be taken This is valuable for comparison with later blood counts

(d) Reports of physical examination and blood counts should become a permanent record

(e) Vacations should not be considered protection against overexposure to radiation

Therapeutic X Ray Installations Operated at Potentials of 400 Kv and Below

1 Equipment

(a) The tube housing shall be a therapeutic type

(b) Permanent diaphragms or cones shall be used for collimating the useful beam and shall afford the same degree of protection as the tube housing Adjustable or removable beam defining diaphragms shall not transmit more than 5 per cent of the useful beam obtained with the maximum treatment filter (See Table 7)

(c) The filter system shall be so arranged as to minimize the possibility of error Filters shall be secured in place to prevent them from dropping out during treatment The filter slot shall be so constructed that the radiation escaping through it does not exceed 1 r/hr at 1 m

(d) The x ray tube shall be centered and mounted so that it cannot turn or slide with respect to the aperture A mark on the housing should show the location of the focal spot Special precautions are necessary if the inherent filtration of the useful beam is very low

(e) Devices shall be provided to immobilize the tube housing during treatment

(f) Open valve tubes may require shielding

(g) A timer shall be provided to terminate the exposure after a pre set time

(h) A beam monitoring device fixed in the useful beam is recommended to indicate any error due to incorrect filter milliamperage or kilovoltage

(i) Lead rubber lead foil etc used for limiting the field should transmit less than 5 per cent of the useful beam (See Table 7)

2 Structural shielding

(a) The required barriers should be a permanent part of the building or equipment Movable lead screens are not recommended and shall not be depended upon above 100 kv

(b) The cost of structural shielding can be reduced considerably by locating the treatment rooms as remotely as possible from occupied areas thus taking advantage of the reduction due to distance (inverse square law) This is particularly true for the higher voltages where thicker barriers are required Corner rooms are especially suited the outside walls and windows do not require any protection if they are sufficiently distant from other occupied buildings and areas Consideration should be given to future occupancy of nearby areas Where most treatments are given with the beam pointed toward the floor special consideration shall be given to the protection of persons habitually in the rooms directly below the treatment room

(c) The control shall be located outside the treatment room for voltages above 100 kv

(d) All wall ceiling and floor areas that can be struck by the useful beam plus a border of at least 1 ft shall be provided with primary protective barriers All wall ceiling and floor areas that because of restrictions in the beam orientation cannot be struck by the useful beam shall be provided with secondary protective barriers

3 Operating methods

(a) The installation shall be operated in compliance with any limitations indicated by the protection survey

(b) No person who works with ionizing radiation shall be in the treatment room during expo-

TABLE 7 —GUIDE TO THICKNESS OF ADJUSTABLE BEAM DEFINING DIAPHRAGMS

Attenuating material	*Approximate thickness of attenuating material necessary for the reduction of the useful beam dose rate to 5 per cent at a potential of —*					
	60 kvp HVL=1 2 Al Filter= 1½ Al[b]	*100 kvp HVL=3 0 Al Filter= 3 Al*[b]	*140 kvp HVL=0 5 Cu Filter= ¼ Cu*[b]	*200 kvp HVL=1 0 Cu Filter= 0 5 Cu*[b]	*250 kvp HVL=3 0 Cu Filter= 3 Cu*[b]	*400 kvp HVL=5 0 Cu Filter= 5 Cu*[b]
	mm	mm	mm	mm	mm	mm
Lead	0 1	0 3	0 7	1 0	1 7	3 5
Brass	3	1 2	4	9	18	

Half value layer in millimeters
[b] Approximate total filtration in millimeters

sure No other person shall be there except when it is clinically necessary If a person is required to hold the patient he shall not be in the useful beam and shall be protected as much as practicable from scattered radiation

(c) Both the patient and the control panel shall be under observation during exposure Provision for oral communication with the patient from the control room is desirable

(d) The useful beam should be directed toward unoccupied areas whenever consistent with therapeutic requirements

(e) The machine shall shut off automatically when the door to the treatment room is opened After such a shut off it shall be possible to turn on the machine only from the control panel Entrances to other areas of radiation hazard should be similarly protected by interlocks

4 Special requirements for x ray therapy equipment operating at potentials of 50 kv and below

(a) Installations shall comply with the general requirements except that the operator is allowed to be in the treatment room during irradiation He shall take special care to avoid exposure to the useful beam Structural shielding generally is not required Because of the short target window distance and low inherent filter the dose rate at the tube aperture may be extremely high

(b) The term grenz ray is used to describe very soft x rays produced at potentials below 20 kv Because of the low penetration of these rays it is not necessary to shield the operator or other persons in the treatment room unless they are exposed to the useful beam at a target distance of less than 3 m However it should be emphasized that grenz rays are x rays and that they may cause the same type of injurious effects as harder x rays although limited to superficial layers of tissue

(c) The term contact therapy is used to describe short-distance irradiation of accessible lesions The potential is usually 40 to 50 kv Because the dose rate at the surface of the window of the tube housing is sometimes as high as 10 000 r/min rigid precautions are necessary to prevent accidental exposure to the useful beam The leakage radiation at the surface of the tube housing shall not exceed 0 1 r/hr If the tube is to be hand held during irradiation the operator shall wear protective gloves and apron When the apparatus is not being used for treatment a cap (0 5 mm lead equivalent) shall cover the aperture window of the tube housing The automatic timer shall be adjustable in graduations at least as fine as 1 sec

(d) Special precautions shall be required in the therapeutic application of apparatus constructed with beryllium or other low filtration windows for both grenz ray and higher kilovoltage therapy As a dose rate of more than 1 million roentgens per minute is possible at the aperture adequate shielding shall be required against the useful beam and special safeguards are essential to avoid accidental exposures

(e) Machines having an output of more than 1 000 r/min at any accessible place shall not be left unattended without the power being shut off first at the control and then at the primary disconnecting means (i e wall plug or main switch) These shall never be turned off in the reverse order

Therapeutic X Ray Installations Operated at Potentials Above 400 Kv

The development and clinical application of supervoltage roentgen therapy with the use of kilovoltages above 1 000 has introduced problems in radiation protection of ever increasing complexity

The National Committee on Radiation Protection recommends [39]

Permanent diaphragms or cones shall be used for collimating the useful beam and shall afford the same degree of protection as the tube housing Adjustable or removable beam defining diaphragms shall not transmit more than 5 per cent of the useful beam For 1 million volt machines this requires approximately 21 mm of lead for 2 million volt approximately 43 mm of lead

* * * * *

All wall ceiling and floor areas that might be struck by the useful beam plus a border of at least 1 ft shall be provided with primary protective barriers *Unless there is reason to assume otherwise* the workload should be taken at the largest value in the second column of Table 9 and this should be multiplied by a use factor of one for the floor one quarter for the walls and one sixteenth for the ceiling and then further multiplied by the occupancy factor for the area that the barrier protects All wall ceiling and floor areas that because of restrictions in the beam orientation cannot be struck by the useful beam shall be provided with secondary protective barriers

PROTECTION AGAINST INJURY FROM RADIUM AND COBALT 60

It should be emphasized that repeated exposure to radium or any radioactive substance even though the exposure is brief will result in some injury and that the effect is a cumulative one

The fatal dose of radium if ingested is usually regarded as 2 μg Evans concluded that about 45 per cent of the total amount of radium in the skeleton and other tissues in cases of chronic radium poisoning gives rise to radon in the expired air that can be measured The remainder of the radium in the body can be determined by the gamma rays

TABLE 9.—PROTECTION REQUIREMENTS FOR THERAPEUTIC INSTALLATIONS

Tube potential	WUT [b]	Useful beam protection: Lead thickness required for primary barrier at a target to occupied area distance of— 5 ft	8 ft	10 ft	15 ft	20 ft	30 ft	Useful beam protection: Concrete thickness required for primary barrier at a target to occupied area distance of— 5 ft	8 ft	10 ft	15 ft	20 ft	30 ft	Distance without barrier [d]	Lead thickness required for secondary barrier at a target to-occupied area distance of— 5 ft	8 ft	10 ft	15 ft	20 ft	Concrete thickness required for secondary barrier at a target to-occupied-area distance of— 5 ft	8 ft	10 ft	15 ft	20 ft
kvcp	ma min per week	mm	mm	mm	mm	mm	mm	in	in	in	in	in	in	ft	mm	mm	mm	mm	mm	in	in	in	in	in
1 000	4 000	125	115	110	100	95	85	31.0	29.0	27.5	25.5	24.0	22.0	700	40	32	28	21	15	13.5	12.0	11.0	9.0	8.0
	1 000	110	100	95	85	80	70	27.5	25.5	24.0	22.0	20.5	18.5	450	28	20	15	12	9	11.0	9.0	8.0	6.0	5.0
	250	95	85	80	70	65	55	24.0	22.0	20.5	18.5	17.0	15.0	290	15	11	9	5	1	8.0	6.0	5.0	3.5	2.0
	60	80	70	65	55	45	35	20.5	18.5	17.0	15.0	13.5	11.5	170	—	—	—	—	—	—	—	—	—	—
	15	55	50	45	35	30	20	17.0	14.5	13.5	11.5	10.0	8.0	90	—	—	—	—	—	—	—	—	—	—
2 000	4 000	240	225	215	205	190	180	51.0	47.0	46.0	43.0	41.0	38.0	1 500	72	56	48	37	30	22.0	19.0	17.0	15.0	13.5
	1 000	215	200	190	180	165	155	46.0	42.0	41.0	38.0	36.0	33.0	1 100	50	37	30	25	20	17.0	14.5	13.5	12.0	10.5
	250	190	175	165	155	140	130	41.0	37.0	36.0	33.0	31.0	28.0	800	30	23	20	15	12	13.5	11.5	10.5	9.0	8.0
	60	165	150	140	130	115	105	36.0	32.0	31.0	28.0	26.0	23.0	500	—	—	—	—	—	—	—	—	—	—
	15	140	125	115	105	90	80	31.0	27.0	26.0	23.0	21.0	18.0	300	—	—	—	—	—	—	—	—	—	—
2 000	500	205	190	180	170	155	145	44.0	40.0	39.0	36.0	34.0	31.0	900	67	52	43	30	23	16.5	14.5	13.0	11.0	10.0
	125	180	165	155	145	130	120	39.0	35.0	34.0	31.0	29.0	26.0	620	43	28	23	17	12	13.0	11.0	10.0	8.0	6.5
	30	155	140	130	120	105	95	34.0	30.0	29.0	26.0	24.0	21.0	400	23	15	12	7	4	10.0	8.0	6.5	4.5	3.5
	8	135	120	110	100	85	75	29.0	25.0	24.0	21.0	19.0	16.0	220	—	—	—	—	—	—	—	—	—	—
	2	110	95	85	75	60	50	24.0	20.0	19.0	16.0	14.0	11.0	120	—	—	—	—	—	—	—	—	—	—

Pulsating potentials require the order of 10 percent less thickness than those given here for constant potentials.

[b] W = workload, U = use factor, T = occupancy factor. Use factor for secondary barrier is always 1. For living quarters the product of workload and occupancy factor shall be multiplied by 4 for computing the protective barriers.

The concrete requirements for this Handbook are based on a concrete density of [illegible]3 g/cm^3.

[d] Distance from target at which the weekly useful beam dose will not exceed 0.3 r.

EDITORS NOTE. Footnotes to table have been abridged.

from its decay product radium C The rate of loss of radium by the patient is directly measured by radium analysis of the feces and urine, in cases of chronic poisoning 0 005 per cent per day is eliminated 91 per cent of this amount in the feces and 9 per cent in the urine The mobilization of radium within the body is studied by quantitative analysis of the source and its filtration The stronger the radioactivity the less time will be needed for the incurrence of injury [18] The safe distance for 1 Gm of completely unprotected radium is about 5 yards but if the radium is enclosed in a container with 5 cm lead walls the safe distance is reduced to about 1 yard

Every radiotherapist who uses radium

Fig 29-3 Lead transportation buggies and hand carriers for radium and radon containers (Courtesy Dr Hugh Scott)

radon present in specimens of alveolar air Simple examination of exposed patients to detect an output of gamma radiation will detect chronic radium poisoning five or six years before any clinical symptoms appear

The distance from the radium containers is one of the most important factors of safety Without intervening lead protection the distance at which radium is dangerous depends in general on the strength of the radioactive should perfect and rigidly observe a non contact technic By the use of suitable instruments such as long forceps it rarely will be necessary to pick up and hold with the fingers any preparation containing radium Provided that adequate precautions in obeying the law of inverse squares are taken a person can handle radium for years without injury but carelessness will produce grave injuries As a rough working rule it should be remembered

that doubling the distance from a radium source is equivalent to increasing the lead protection by 3 cm

Attention should be called to the fact that protection values of lead against roentgen rays do not apply to gamma rays Materials lighter than lead are normally more effective against gamma rays than against roentgen rays In general it is accurate to assume that the absorption is proportional to the density and

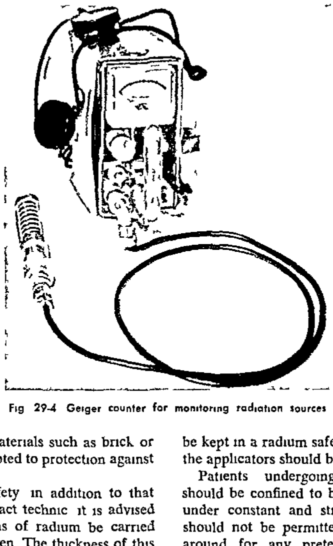


Fig 29-4 Geiger counter for monitoring radiation sources

therefore building materials such as brick or concrete are well adapted to protection against gamma rays

As a factor of safety in addition to that offered by a noncontact technic it is advised that all manipulations of radium be carried on behind a lead screen The thickness of this screen depends on the quantity of radium to be handled The arms of the technician should work around a thick L shaped lead screen the vertical leg of the screen protects his thorax and the radium lies on the horizontal leg of the screen

In those instances in which it becomes necessary to transport radium or radon any distance for treatment of a patient the radioactive applicator should be carried in a closed lead box of appropriate thickness The radioactive substance should never be held above the level of the knees The importance of keeping away from radium is the prime consideration

As there is the danger of possible injury to the health of some unsuspecting person when an applicator is not in its proper place it is essential that all applicators when not in use be kept in a radium safe and a daily check of the applicators should be made

Patients undergoing radium treatment should be confined to bed or otherwise kept under constant and strict surveillance they should not be permitted to leave and stroll around for any pretext whatever In the event that the applicator slips out of position during treatment the nurse in charge of the patient should call the radiologist at once On the completion of treatment no bandages or dressings used by the patient should be destroyed until the radium applicator has been checked and the radium stored in the safe

When radium treatment must be given in

the large wards it is desirable to tie onto the patient's bed a large tag that warns all the inmates and personnel to keep away from possible injury at the same time the tag prevents diversion of the nurses attention to less important matters All details of the treatment should be left to a nurse from the radium department and should not be entrusted to nurses on general duty

bination of the following factors (a) increasing the working distance from the source of radiation (b) reducing the time of exposure and (c) interposing attenuating (protective) barriers between the source of radiation and persons The first of the *fundamental factors* the distance includes the inverse square law and to a lesser extent the reduction due to the air absorption The air absorption is small for gamma radiations considered here but is very large for particulate radiation

Because of the short ranges of alpha particles

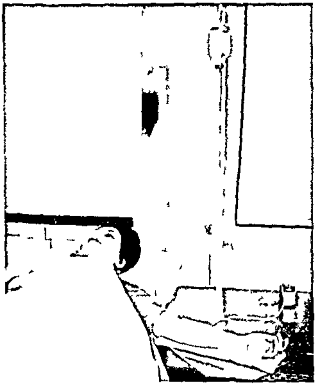


Fig 29 5 A method of administering systemic radioactive isotopes that protects the personnel

no protection is required against them when the source remains intact While beta particles have considerably longer paths in air than alpha particles they are easily stopped by thin layers of metal or plastic Usually such a layer is incorporated in the capsule sealing the source Protection against gamma rays because of their much greater penetration requires more detailed consideration and the barriers required are much more expensive

RECOMMENDATIONS OF NATIONAL COMMITTEE ON RADIATION PROTECTION ON PROTECTION FROM INJURY BY RADIUM AND COBALT 60

The following are excerpts from the National Bureau of Standards handbook [37] which deals with protection against radiations from radium cobalt 60 and cesium 137

Basic Principles of Radiation Protection

The ultimate purpose of all radiation protection measures is to maintain the dose received by persons at no more than the applicable maximum permissible levels and to prevent damage or impairment of function of radiation sensitive films other objects and instruments The dose received by persons may be reduced by any one or a com

Useful beam The primary protective barrier thickness may be obtained from [transmission data of radium cobalt 60 and cesium through concrete iron and lead [37]] if the permissible transmission of radiation is known

The permissible transmission H may be calculated from

$$H = \frac{0.3D}{W T} \qquad (1)$$

where 0 3* is the maximum permissible weekly exposure in roentgens D is distance from source to position in question in meters W is total weekly exposure in the useful beam at 1 m from the source (obtained by multiplying the roentgens per minute at 1 m by the weekly irradiation time in minutes) and T is occupancy factor the fraction of weekly irradiation time during which a person is exposed

Leakage radiation Equation (1) may be used to compute the barrier requirements for this radiation where W is the leakage radiation in roentgens per week measured at 1 m from the source

Scattered radiation Radiation scattered from an irradiated object has a lower dose rate and is softer (of lower energy) than the incident beam Both the energy and dose rate of the scattered beam vary with the angle of scattering However for moderate sized fields and scattering angles greater than 90 deg it has been shown that the dose rate of the scattered radiation (measured at 1 m from the scatterer) is less than 0 1 per cent of the weekly exposure at 1 m from the source for most practical cases The barrier required for 90 deg scattered radiation may be obtained from [tabulated data [37]] if the permissible transmission of radiation by the barrier is known The permissible transmission B may be calculated from

$$B = \frac{0\ 3S^2}{0\ 001WT} \quad \text{or} \quad \frac{300S^2}{WT}, \qquad (2)$$

where 0 3 [0 1] is the maximum permissible weekly exposure in roentgens S is distance from scatterer to position in question in meters W is total weekly exposure in the useful beam at 1 m from the source (obtained by multiplying the roentgens per minute at 1 m by the weekly irradiation time in minutes) and T is occupancy factor the fraction of weekly irradiation time during which a person is exposed

Secondary protective barriers The rules given above for scattered radiation and for leakage radiation may be used to compute the secondary protective barrier thickness for each of the two separate effects If the barrier thicknesses so computed separately are nearly equal (that is differ by less than 3 HVL) then 1 HVL should be added to the larger single barrier thickness to obtain the required total But if one of the thicknesses is more than 3 HVL greater than the other the thicker one alone is adequate

Shielding If the shielding is adequate for the useful radiation it is also sufficient for leakage and scattered radiation It should be determined however that radiation scattered around the end of the primary protective barrier does not cause a radiation hazard

For reasons of economy barriers should be placed as near to the source as possible The barrier thickness is not reduced by this procedure but the area and therefore the volume are reduced the barrier weight is approximately proportional to the square of the distance between the source and barrier

Concrete marble and similar materials generally provide the most economical barrier but lead may be required where the space is limited or where it is desirable to reduce the weight

All openings in barriers such as for doors windows pipes etc shall be provided with at least the radiation protection required for the surrounding barrier

Joints between the same or different kinds of protective material shall be so constructed as to provide the same protection as that required of the adjacent material

EDITORIAL NOTE Consideration is being given toward reducing this value for the maximum permissible weekly exposure and future reference to this value should take any such change into consideration

Equipment and Facilities for Handling, Storage, and Transportation

The equipment and facilities discussed in this section refer only to sources of intermediate curiage [millicurie] Microcurie and kilocurie sources are excluded.

Handling Equipment

* * * * *

L block The preparation and dismantling of applicators incorporating sources or similar operations shall be carried out behind a protective L block of such size and thickness as will adequately shield the operator The block should have the following characteristics

(a) The top should be provided with an inclined high density transparent visor or an alternate arrangement for viewing

(b) The side next to the operator should have a protective pad to keep his body at least 30 cm from the point where the source is handled or the block should be so placed on the working table as to accomplish the same result without such pad

(c) The inside corner of the L should preferably be curved

(d) For the usual L block having a minimum lead equivalent of 5 cm the following maximum weekly millicurie hours at a distance of 30 cm are permissible radium 160 mc hr cobalt 60 100 mc hr cesium 137 360 mc hr

(e) A lead lined well" or its equivalent should be provided near the L block so that the required radioactive sources can be held therein during the preparation of an applicator

NOTE The maximum weekly permissible dose of 1 5 r to the unshielded hands determines the above limits The weekly dose to the part of the body shielded by the L block is less than one third of the 300 mc maximum permissible dose *

EDITORIAL NOTE These values are gradually being scaled lower

Fig 29-6 Argonne National Laboratory's Master Slave Manipulator designed for the safe handling of radioactive materials (Courtesy Argonne National Laboratory)

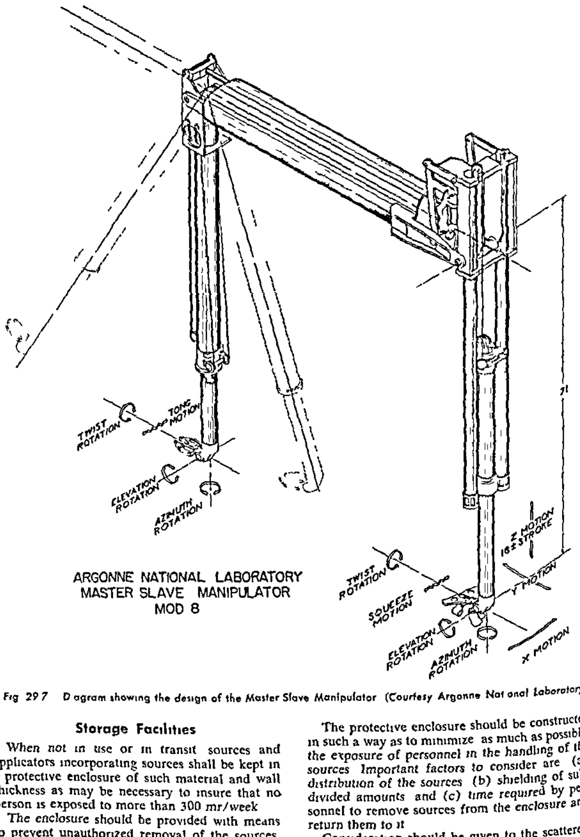


Fig 29 7 Diagram showing the design of the Master Slave Manipulator (Courtesy Argonne National Laboratory)

Storage Facilities

When not in use or in transit sources and applicators incorporating sources shall be kept in a protective enclosure of such material and wall thickness as may be necessary to insure that no person is exposed to more than 300 mr/week

The enclosure should be provided with means to prevent unauthorized removal of the sources

The protective enclosure may be advantageously located near the preparation work bench to reduce the exposure of personnel during transfers of sources

The protective enclosure should be constructed in such a way as to minimize as much as possible the exposure of personnel in the handling of the sources Important factors to consider are (a) distribution of the sources (b) shielding of subdivided amounts and (c) time required by personnel to remove sources from the enclosure and return them to it

Consideration should be given to the scattered radiation It is not sufficient to place large sources behind a barrier no matter how thick if the radiation scattered around it presents a hazard Where a large number of sources are stored a

lead lined safe with lead filled tays may be used to advantage This permits the individual sources to be stored in holes in the lead of the trays

Separate compartments should be provided for different types of sources

Each compartment should be marked so as to permit immediate and certain identification of its contents from the outside It is highly desirable that tubes cells needles, etc be readily identifiable from a considerable distance as to their type and activity When sizes and shapes are not adequate other means should be employed

The protection of the individual compartments and enclosures as a whole should be such that a person standing in front of the enclosure in performance of his duties receives in that time only a small fraction of the permissible dose

Transportation Facilities

Intramural transport carriers Transportation of radioactive sources within an institution should be done only by means of adequately shielded carriers In general lead is the most practical shielding material for carriers

Transportation by private car During transportation of radioactive sources by private car (such as by physicians in practice) the source should be in a transport carrier offering adequate shielding to all occupants of the car

The carrier should be located as remotely as practicable from occupants It should be suitably marked with the name and address of the owner a notice that the contents may be dangerous if removed and that the owner should be notified if the carrier is found

If it is necessary to leave radioactive materials in an unattended car the container shall be locked in the car preferably in the luggage compartment

Any loss or theft of radioactive material that may constitute a potential public hazard should be reported immediately to the local police or public health authorities

Public transport containers The public transportation of radioactive materials is subject to federal state and local regulations

Those responsible for the shipment of sources should be familiar with the current regulations of the Interstate Commerce Commission Post Office Department and Civil Aeronautics Board

Medical Applications—Interstitial, Intracavitary and Surface

In the medical applications of radioactive sources there are five operational stages during which radiation hazards may exist

(a) Transfer of sources from storage and preparation for use on patients

(b) Transfer from preparation bench and application to patient

(c) Irradiation of patient

(d) Removal of sources from patient and transfer to preparation bench

(e) Removal of sources from applicators cleaning and transfer from preparation bench to storage space

Each of these stages and each type of source presents peculiar problems [EDITORS NOTE Each is considered individually in National Bureau of Standards handbook on Protection Against Radiations from Radium Cobalt 60 and Cesium 137 [37]]

Precautions While Source Is in or on the Patient

The bed cubicle or room of the hospital patient should be marked with a tag or sign stating what radioactive substance is being used the number and nature of the sources the total amount of material the time and date of application and anticipated removal instructions to nurses and any remarks that would enable the source custodian to retrieve sources If the curiage of the sources is so dangerously large that occupancy of surrounding areas should be restricted a special tag should indicate the danger range to discourage persons from remaining in the area unnecessarily

The extent to which the patient with radioactive material must be segregated depends upon the type of source and the total curiage its location on the patient how long it is to be on him how long his neighbors stay near him per week and to what other exposure those neighbors (patients or nurses) are subject Table 7 gives the distances for various millicurie hours of radium cobalt 60 and cesium 137 at which a person will receive the maximum permissible weekly exposure of 0 3 r

Patients with removable sources in or upon their persons should not be permitted to leave the hospital or clinic

TABLE 7—RELATION BETWEEN DISTANCE AND MILLICURIE HOURS FOR AN EXPOSURE OF 0 3 r FROM AN UNSHIELDED SOURCE

Millicurie hours	*Distance to source*		
	Radium	*Cobalt 60*	*Cesium 137*
	ft	ft	ft
10	0 5	0 7	0 4
30	1 0	1 2	0 6
100	1 8	2 2	1 2
300	3 0	3 8	2 1
1 000	5 5	7 0	3 7
3 000	9 5	12	6 5
10 000	18	22	12

Protection Surveys

An initial survey should be made of any facility to be used for the handling or storage of radioactive sources This survey should include all storage containers transport carriers shields and teletherapy equipment The survey should be made by or under the supervision of a qualified expert who shall submit a suitable written report

If any changes are made in the layout or shielding or if there is a possibility of a fault developing through cold flow in metallic shielding or through wear the survey should be repeated at appropriate intervals Such surveys should be the basis of limiting time of occupancy of certain areas or performance of certain duties if necessary

For conditions where the dose rate is expected to be low films may be used in making an approximate survey If indicated a survey should then be made with suitable instruments

Ionization chamber measurements are required only if a prior scanning with a suitably calibrated Geiger Mueller or scintillation type of instrument indicates occupied regions to have a radiation level of more than one fifth of the permissible dose rate

Radium Leakage

All radium sources should be tested for contamination upon receipt if facilities are available Sources certified by the National Bureau of Standards are so tested at the time of certification If there is reason to believe that a source has been damaged it shall be tested for leakage If facilities are not available locally it shall be sent to a qualified laboratory for test

To test for leakage a Geiger Mueller or scintillation counter or an alpha survey instrument is required Each radium source to be tested can be placed close to or wrapped in an absorbent material such as cotton or filter paper and left for at least a day preferably in a small sealed container The absorbent material should then be checked for contamination with a suitable instrument The presence of contamination indicates a leak If radium leakage is gross or has existed for some time merely wiping the source and testing the wipe should show contamination This is also true for cobalt 60 and cesium 137 sources

Sources that leak shall be placed in sealed containers and can be sent to a qualified laboratory for repair and measurement Containers and carriers as well as any other equipment that has had contact with the leaking source shall be decontaminated under the direction of a qualified expert

Radiological Safety Officer

In every hospital clinic or laboratory handling radioactive sources there shall be a radiological safety officer The radiological safety officer shall be responsible for the establishment of satisfactory working conditions according to current standards

Any region that is easily accessible and that cannot be continuously occupied without exceeding the maximum permissible dose should be posted to warn all concerned that this is a dangerous area This specifically applies to regions where sources are stored or handled and areas where patients are being treated The combination of the permissible working distance from the source and the exposure can be determined from Tables 8 and 9

TABLE 8 —PROTECTION REQUIREMENTS FOR RADIUM IN CENTIMETERS OF LEAD

Milligrams of radium	*Thicknesses of lead required at a distance of —*		
	30 cm	1 m	2 m
	48 HR/WEEK		
	cm	cm	cm.
25	6 6	1.9	0
50	8 1	3 3	0 7
75	9 0	4 0	1 3
100	9 6	4 6	1 9
200	11 1	6 0	3 3
	12 HR/WEEK		
25	3 8	0	0
50	5 2	0 7	0
75	6 1	1 3	0
100	6 6	1 9	0
200	8 1	3 3	0 7
	6 HR/WEEK		
25	2 5	0	0
50	3 8	0	0
75	4 6	0 3	0
100	5 2	0 7	0
200	6 6	1 9	0

Emergency Care for Possibly Contaminated Persons

All suspected persons should be surveyed for radioactive contamination

If no monitoring instrument is available all possibly exposed persons should be regarded as contaminated Wipes from various parts of the bodies of these persons and their clothing should be made with some type of disposable tissue filter paper or blotting paper and the samples placed in separate labeled envelopes for future study

Contaminated persons should remove all clothing carefully and place it in some type of disposable container or bag If this is not available

clothing should be put on paper to prevent contamination of floor and furniture This can be monitored later to determine the possibility of decontamination or the need for disposal

TABLE 9 —PROTECTION REQUIREMENTS FOR COBALT 60 IN CENTIMETERS OF LEAD

Cobalt (rhm)	*Thicknesses of lead required at a distance of —*		
	30 cm	1 m	2 m
	48 HR/WEEK		
	cm	cm	cm
0 1	9 4	5 5	3 0
0 3	11 3	7 5	5 0
1 0	13 4	9 5	7 1
3 0	15 4	11 4	9 0
10 0	17 7	13 6	11 1
	12 HR/WEEK		
0 1	7 0	3 0	0 6
0 3	8 9	5 0	2 6
1 0	11 0	7 2	4 7
3 0	13 0	9 1	6 6
10 0	15 1	11 1	8 6
	6 HR/WEEK		
0 1	5 8	1 8	0
0 3	7 7	3 9	1 3
1 0	9 7	5 9	3 5
3 0	11 7	7 8	5 4
10 0	13 9	10 0	7 5

Contaminated persons should then be covered with some type of emergency clothing and taken to a shower area for bathing

Bathing should be done under showers and commercially available detergents and soaps can be used Several separate washings should be performed Highly alkaline soaps abrasives organic solvents or cleaners that tend to increase permeability of the skin should not be used Special emphasis should be given to cleaning of fingernails toenails nostrils scalp ears and body folds

Scrub brushes should be used but care should be taken that the skin surfaces do not become abraded

After the body is well washed the person should be surveyed with a suitable monitoring instrument and additional smears taken with disposable tissues cotton tipped applicators or filter paper The ear canals and nostrils should be swabbed for contamination Smear tests are especially important if alpha survey instruments are not available Fresh clothing should be put on

Small cuts and other breaks in the skin surface should be sought for carefully since absorption of isotopes can occur by this route Such lesions should be decontaminated after the above washes by repeated 5 min scrubs after removal of scabs and crusts

A physician should be called immediately to carry out the following medical studies on contaminated persons

(a) Complete medical history and physical examination with special emphasis on previous occupational history and possible exposure to radiation should be secured A chest roentgenogram should be obtained

(b) Complete blood count including hematocrit reading and routine urinalysis should be done

(c) Quantitative collection of urine should be made for the first 72 hours for assay of the isotope Each day s specimen should be put in a separate container These specimens may be collected in bottles containing 10 ml of dilute nitric acid (approximately 10 ml of concentrated nitric acid per liter of water) for each 24 hr specimen An additional 10 ml of concentrated nitric acid should be added to the specimen after the collection is complete

(d) Feces should be collected for the first 72 hours for determination of radioactivity Each day s specimen should be put in a separate container These can be collected in round 1 qt (1 liter) ice cream containers

(e) Breath samples should be taken for radon if the accident involves radium

(f) Arrangement should be made for surveys of the total body gamma radiation with a sensitive measuring device

(g) Within 72 hours blood should be taken in 20 ml samples for determination of radioactivity

(h) The specimens of urine feces and blood should be refrigerated and kept until arrangements can be made for analysis at a qualified laboratory Proper collection and storage of these samples will be of great value to the contaminated persons and also in obtaining future data concerning the metabolism of the isotopes involved

Special Problems

Radium The chief hazard of radium is the danger of retention of long lived alpha emitting isotopes in the body The amount of retention depends in part on the salt of radium used The insolubility of radium sulfate tends to permit less absorption in the body than in the case of the more soluble radium chloride and radium bromide

Treatment for radium retained within the body should be carried out as follows

(a) Gastric lavage with 10 per cent magnesium sulfate solution should be done as soon as possible

(b) Daily purging with saline cathartics will tend to promote excretion of radium from the gastroenteric tract and this type of cathartic will act as a mild stimulant to bile production Since

absorbed radium is excreted to a large degree in the bile such therapy may be of some value Administration of magnesium sulfate is suggested since it will tend to precipitate soluble radium ions in the form of the insoluble sulfate

(c) If cuts and other skin lesions cannot be adequately decontaminated surgical excision of the area should be considered

Other isotopes Certain other radioactive isotopes are now being used widely both in sealed containers for local irradiation therapy in millicurie quantities and also in teletherapy installations in kilocurie amounts

(a) *Cobalt 60* The hazard of spillage from cobalt 60 is relatively small If Co^{60} sources are not sealed in containers or adequately plated with gold or other coating some contamination may result from oxidation or corrosion of cobalt No attempt should be made to remove the protective plating of Co^{60} except by qualified laboratories

The general procedures to be followed in the event of spillage have been described Decontamination is best carried out by the use of various complexing agents such as the versenes used with detergents If Co^{60} is introduced through the skin areas of local inflammation and possibly sterile abscesses may result Some Co^{60} will be carried to the liver and kidneys also After oral ingestion in rats Co^{60} is poorly absorbed from the blood stream via the urine and bile

(b) *Cesium 137* This isotope is usually produced as powdered Cs_2SO_4 and then is utilized in a sealed container The radiation stability of cesium 137 must be carefully evaluated since certaine cesium salts decompose with evolution of oxygen Therefore the hazards are similar to those of radium except that cesium is not a bone seeker

Little is known of the metabolism of Cs^{137} Studies in rats show that oral absorption is 100 per cent with 45 per cent being deposited in muscle The half time of elimination from muscle is 15 days $Cesium^{137}$ given parenterally follows the same metabolic pattern The rate of elimination is very much greater than its rate of radioactive decay

If Cs^{137} escapes from a sealed container decontamination can be done with aqueous solutions of detergents or dilute nitric acid

Loss of sources

(a) Any loss of a source shall be reported immediately to the radiological safety officer

(b) All linen dressings clothing and equipment shall be kept within the cubicle or room of a patient until all sources are accounted for

(c) Each institution should have available one or more portable instruments capable of detecting gamma activity of less than 1 mc at 10 ft. Usually instruments of the ionization-chamber type are less sensitive but more rugged than survey meters using Geiger Mueller or scintillation counters Geiger Mueller survey instruments when used in fields of high radiation intensity may fail completely to respond and thus give inexperienced persons a false sense of security

CHAPTER 30

The Treatment of Radiation Reactions

Ruth J Guttmann

INTRODUCTION

The treatment of local portal reactions after irradiation follows certain principles that vary only when an overdose instead of a tolerance dose of radiation therapy has been administered

An appreciation of the tissue reactions will permit a better understanding of the principles of their treatment The reactions of tissues within a beam of ionizing radiation depend upon the type and amount of irradiation and are influenced by such factors as voltage filtration size of portals and the time intensity factor

The Effects of Voltage and Filtration Upon Reaction to Irradiation

Table 30 1 presents the skin erythema dosages for the various voltages and filtration

Influence of the Size of the Treated Region upon the Tissue Reaction

The size of the field is in direct proportion to the reaction the larger the field the more severe the reaction Accordingly every effort must be made to keep the portal as small as is consistent with desired effect upon the neoplasm being treated If opposing fields are used the exit dose must be added to the skin dose on each side to compute total dose to each area

Time and Intensity Factors and Their Effects Upon Radiation Reactions

Biologic reactions are more marked if a given amount of radiation is delivered in a short interval than if the same dose is extended over a longer period The concepts of protraction—the rate at which radiation is administered during a single exposure and fractionation—the number of exposures delivered over an extended period have been illustrated graphically by Strandquist

The basis for the protracted and fractionated technic in radiotherapy is that normal healthy tissue recovers from injury more rapidly by this technic whereas tumor destruction continues

TABLE 30 1 —Threshold Erythema Doses for Various Qualities of Radiation

Kv	*H V L*	*Roentgens for threshold erythema dose including backscatter*
100	1 0 Al	270
140	0 4 Cu	525
200	0 9 Cu	680
700	7 0 Cu	800
1 000	3 8 Pb	1 000

THE NATURE OF LOCAL RADIATION REACTIONS

Radiation Reactions Subsequent to Tolerance Dose

Skin Reactions The sequence of events that follow irradiation is unique When overwhelming doses are administered at one sitting a reaction may present itself quickly Usually, however, no visible reaction occurs for a period varying from 5 to 10 days Following this latent period a faint blush will present itself on the skin, it gradually increases

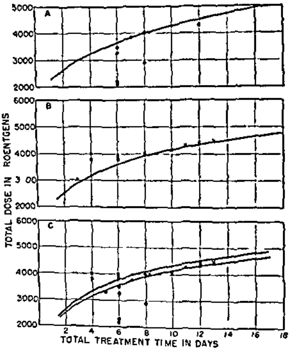


Fig 30 1 Influence of time factor and intensity of irradiation on biologic react on (Courtesy Dr Edith Quimby)

in intensity until a scarlet red color is present (erythema) The coloration persists for a brief period of from 1 to 3 weeks The erythema is due to an increased flow of blood through the blood vessels of the area as well as to an increase in the number of capillaries carrying blood In more severe reaction an extravasation of blood from the vessels into the surrounding tissues develops The coloration persists for a brief period of from 1 to 3 weeks and may disappear later When maximal tolerance doses are given the superficial epidermis breaks and a moist weeping surface with a serofibrinous exudate presents itself (desquamation) It lasts from 1 to 3 weeks The area is denuded of epidermis and presents a tender, weeping granular surface Epithelization occurs if the tissues are not traumatized or irritated A brown pigmentation may persist The degree and extent of this reaction are influenced by various factors (1) Variations in skin tolerance itself fair skin being more sensitive than dark skin, (2) the region of the body treated thinner skinned areas being more sensitive than thicker ones moist areas being more sensitive than dry ones (3) the blood supply of the treated area, local anemia increasing the skin tolerance hyperemia decreasing it

Hair bearing regions have their specific reactions Epilation occurs after small amounts of irradiation but it is rarely permanent The hair grows again even after a high dosage though it may take several months or years.

The reaction in the *mucous membrane* differs from that of the skin The period of the latent reaction is shorter the erythema lasts only a few days and is followed by a greyish white membrane covering the irradiated zone which persists during the course of treatment *Reactions of skin and mucosa are painful It is important to realize that mucosal reactions sometimes reach a peak when only about 50 per cent of the irradiation has been given and frequently decrease though treatment is continued to the desired level* It would be a mistake to stop therapy in order to relieve symptoms that are unavoidable and will decrease even during the course of therapy The reactions of mucous membranes are associated with specific symptoms of the involved organs

Oral pain is to be expected when a carcinoma of the tongue is being irradiated dryness of the mouth whenever salivary glands are being exposed to more than 1 000 r When in treatment of neck tumors radiation of the pharynx cannot be avoided dysphagia occurs. When the larynx is irradiated hoarseness occurs Edema of laryngeal structures may be of such severity as to cause respiratory obstruction and tracheostomy must be performed

Chest pain with an associated irritating cough and dysphagia may occur when the trachea and esophagus have been exposed to irradiation In pelvic irradiation bladder and

bowel reactions will occur Dysuria and polyuria may require treatment especially when aggravated by a concurrent infection Diarrhea the first sign of bowel irritation may become so severe that treatment must be temporarily abandoned Another absolute indication for interruption of therapy is the occurrence of bloody mucus

In contrast to these changes which consist of a cycle of damage *and* repair in the generative tissues more severe changes owing to irradiation overdosage develop

Fig 30-2 Erythema after 4 000 r measured on skin given through a 10 × 10 cm field in 21 elapsed days This photograph was taken on the last treatment day Radiation factors were 250 kv HVL 2 8 mm Cu 50 cm TSD

Fig 30-3 Two weeks after complet... same *patient now* shows moist desq... ...ning spotty epithelization

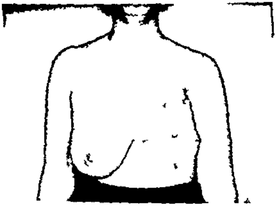


Fig 30-4 Tanning of the skin in a female two months after completion of therapy with the same factors listed for the patient in Figures 30-2 and 30 3

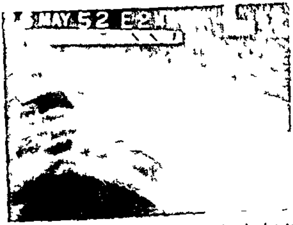


Fig 30 5 Pathologic fracture of left clavicle due to radiation reaction given *many years* before for treatment of cancer of the *breast* (Courtesy Drs George T Pack and Irving M Ariel)

Local Radiation Changes Due to Overdosage of Irradiation

The reactions of skin and mucous membranes follow at first the same pattern owing to tolerance dose Following this first stage induration in the treated region occurs which is either covered by smooth atrophic skin or by a shiny mucous membrane Fibrosis and extensive telangiectasis will develop if necrosis does not supervene These tissues have tendency to break down at the slightest provocation

Tissue necrosis develops In the ... it may run through different stages which are accepted as physiologic reactions to irradiation within tolerance Erythema will be followed by moist desquamation that fails to heal and usually an indolent painful ulcer develops with sharply cut edges and a sloughing base Late necrosis with formation of the same type of indolent ulcer may occur at any time after treatment even after several years It occurs ordinarily as sequence to *trauma* or by exposure to excess *cold or heat* It is essential to differentiate a recurrence of the

Treatment of Damage Due to Overdosage

Treatment of changes due to overdose follows two different lines Tissues in which necrosis might occur but has not are to be guarded with utmost care and even minimal trauma must be avoided The approach changes when one deals with established necrosis

In lesions of the skin dressings with Furacin Scarlet red vitamin A and D ointment are indicated as support of the healing and cleaning process while Chloresium dressings decrease offending odors Antibiotic ointments (neomycin bacitracin etc) supplemented with parenteral antibiotics should be used to control local infection More active methods such as electrocoagulation or wide surgical excision of the necrotic area are at times indicated

Necrosis of the mouth affects soft parts with or without damage to the underlying bone The treatment varies accordingly The rules given in the treatment of acute reactions in the mouth must be strictly observed Additional therapeutic measures are in most cases necessary owing to the extreme painfulness of these necrotic sites Often only the application of anesthesizing sprays makes it possible for the patients to chew and swallow food otherwise they would succumb to malnutrition and exhaustion

As a last resort in the treatment coagulation of the necrotic lesion is indicated with the intent to destroy all the sensitive nerve endings that are embedded between the fibrous tissue at the hard edges of the necrotic ulcer and are the cause of the excruciating pain

Bone necrosis in the mouth may occur in some cases beneath unbroken mucous membrane No other symptoms may be present but the patient complains of severe pain similar to an agonizing toothache Part of the bone will slowly degenerate and die after endarteritis has destroyed the blood supply and the dead bone will form a sequestrum In other patients the process starts with a necrotic ulcer in the overlying mucous membrane while necrotic bone can be felt afterward in the depth of the ulcer It is always essential to be conservative until the sequestrum separates spontaneously as any premature surgical interference would cause an extension of the necrotic process in the adjoining bone When the sequestrum has separated spontaneously it can easily be removed The healing process starts immediately the patients show striking improvement and feel free of pain and the entire necrotic area is replaced by a scar in a relatively short time Whenever in rare cases a salivary fistula forms after necrosis of the mandible spontaneous healing is impossible and surgical repair is necessary

Pathologic fractures of the clavicle ribs and neck of the femur usually do not occur before one year after completion of therapy Their first and only symptom is pain, which precedes the establishment of the roentgenologic diagnosis The treatment is conservative by rest or fixation For fractures of the neck of the femur bed rest alone is the treatment if there is no displacement of the fractured bones but internal fixation subtrochanteric osteotomy or reduction with immobilization will become necessary if the displacement of the fragments so requires The results of therapy are good even in the group of fractures with gross displacement

It is essential to distinguish a fracture the late sequel of irradiation from metastatic cancer For neoplasms such as those arising in the breast where the occurrence of late osseous metastases is not uncommon it is at times difficult to distinguish metastatic cancer from irradiation fracture In the former additional irradiation may be indicated whereas in the latter it is definitely contraindicated

Cartilage necroses are best removed surgically as they are always extremely painful and usually occur in places that can be readily approached by surgery

INTESTINAL INJURIES

The treatment of late intestinal injuries following irradiation is conservative observation as patients may be asymptomatic for long periods in spite of marked pathologic changes However they must be under constant care and observation as the disease is progressive In spite of relative subjective well being these patients may be subject to intestinal hemorrhage perforation with generalized peritonitis or obstruction These

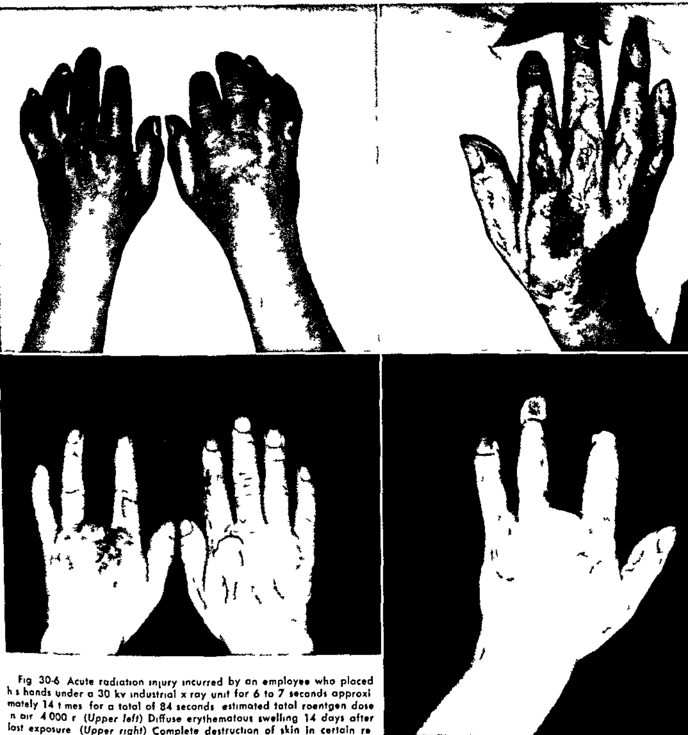


Fig 30-6 Acute radiation injury incurred by an employee who placed his hands under a 30 kv industrial x ray unit for 6 to 7 seconds approximately 14 times for a total of 84 seconds estimated total roentgen dose in air 4 000 r (*Upper left*) Diffuse erythematous swelling 14 days after last exposure (*Upper right*) Complete destruction of skin in certain regions with atrophy of underlying tissue 1 month after exposure (*Lower left*) Status 10 months after exposure: middle finger of left hand has been amputated Remainder of hands atrophic with stiffeni due to underlying fibrosis Free skin grafts have been used to cover the regions of destroyed skin (*Lower right*) Status 23 months af exposure progressive atrophy especially marked of the three digits of the left hand Further radiation changes occurred necessitati additional surgical removal and skin grafting (*Courtesy Drs Irving M Ariel George T Pack and Robert J Booher*)

facts and considerations give rise to the question whether a patient would not benefit more from elective surgery with a higher percentage of survival and better quality of surgery compared with emergency operations and their handicaps

Wiley and Sugarbaker have described small bowel reactions and the following discussion summarizes their findings

The pathologic findings at operation or at autopsy are remarkably constant The peritoneum has lost its luster and is thickened Obstruction if present is usually in the distal portion of the ileum with a loop or loops of small intestine fixed in the pelvis Other segments may show greyish white mottled avascular serosa with interspersed telangiectatic regions There may be necrosis and if perforation has occurred localized or generalized peritonitis Regions of ulceration will be found on the mucosal surface with fibrosis to the point of obstruction in some segments

Only those segments of small intestine that can fall into the pelvis are affected when the damage results from irradiation to pelvic structures (cervix) The rectum and sigmoid often present a similar picture

The fibrosis and edema eventually result in a state that may aptly be termed insufficiency of the small bowel The muscularis is largely replaced by fibrosis and that which remains is handicapped by the accompanying edema and induration Radiation therapy produces the initial changes but infection and possible trauma are necessary for the continuation of the process The use of multiple ports and heavy filtration for deep seated tumors has resulted in relatively slight skin injury but the deep tissue may be severely irradiated This is especially prone to destroy the intestinal epithelium which has been considered as sensitive as are the lymphocytes in this same region

Factitial reaction of the small intestine occurs usually in small thin women Diarrhea usually occurs during therapy

Treatment

These patients present difficult therapeutic problems They are chronically ill individuals with marked weight loss anemia and hypoproteinemia Most of them have been unable to take an adequate diet for several months and with the damage to the small bowel have probably not been able to absorb properly all the food that was taken The condition is not unlike idiopathic ulcerative colitis with small bowel involvement or regional ileitis and many of the therapeutic procedures both medical and surgical used in these two conditions are of value in the treatment of factitial disease of the intestines Treatment may be either medical or surgical or a combination of the two

Medical In the treatment of the malnutrition and weight loss a bland low residue high protein high caloric diet supplemented by brewer s yeast and parenteral vitamins should be given If there is considerable cramping pain antispasmodics such as tincture of belladonna atropine or papaverine are of value If diarrhea is a prominent symptom bismuth subcarbonate or paregoric is useful Multiple transfusions are usually necessary to correct the anemia and probably constitute the best method with the exception of a high protein diet for correcting the hypoproteinemia If there are signs of sepsis succinylsulfathiazole penicillin and/or sulfadiazine have proved of value

Surgical When medical management does not relieve these patients or when signs of obstruction develop surgical intervention must be considered It is of note that radiation ileitis frequently produces intestinal obstruction necessitating surgical intervention Factitial proctitis and sigmoiditis rarely produce intestinal obstruction and except for two or three cases have responded to medical management

Preoperatively these patients should be properly hydrated anemia corrected by blood transfusions and sepsis treated by means of antibiotic drugs A Miller Abbott tube should be passed in those cases with partial or complete intestinal obstruction The use of this tube makes it possible to delay operation until the general condition of the patient has improved Preoperatively the rectum should be observed through the proctoscope to determine if it as well as the small intestine is damaged If it is an ileostomy or colostomy may be indicated

The decision as to what *surgical procedure* is to be carried out on each patient depends

upon the findings at operation correlated with the preoperative roentgen ray findings and requires considerable surgical judgment We feel that any surgical procedure undertaken should be as conservative as possible, since without exception these patients have been extremely poor surgical risks In general no attempt should be made to free the damaged adherent small bowel but a simple sidetracking anastomosis should be made between healthy loops of small intestine or between the small bowel and colon Any anastomosis must be made between normal appearing loops of intestine since the radiation damaged bowel heals poorly

Since it is usually the terminal loops of ileum that are damaged or obstructed the most useful anastomosis has been an ileocolostomy The Mikulicz double barrel type of anastomosis is preferred for three reasons (1) It can be done extraperitoneally thus eliminating the serious danger in these cases of suture line leakage and peritonitis This is essential because of the poor healing of irradiated bowel (2) Since often there is an associated distal large bowel factitial reaction the colon can be put at rest for a few months or if necessary for years by this procedure (3) The operation is usually performed in the face of intestinal obstruction and immediate decompression is desirable This procedure makes this available at once The value of an ileostomy in this condition can be likened to its value in ulcerative colitis if both the large and the small bowel are damaged

In general there is so much damage to the intestine and the condition of the patient is so poor that if resection is attempted it becomes a major and frequently shocking procedure It is generally contraindicated

Four patients with this condition who were autopsied by Wiley and Sugarbaker revealed no evidence of carcinoma

RADIATION INJURIES OF THE URINARY TRACT

Radiation injuries of the urinary tract manifest themselves as indolent ulcers of the bladder vesicovaginal fistulas or stricture of the ureter with secondary hydronephrosis The onset of the symptoms—bladder symptoms or pain in the flank—may be sudden or more insidious Conservative treatment with instillation of Argyrol is the method of choice for ulcers of the bladder but stricture of the ureter and hydronephrosis must be approached surgically

EDITORIAL ADDENDUM

Systemic reactions to irradiation vary with the type of radiation the speed with which the ionizing radiations are administered the quantity of radiation absorbed by the body and the amount of the body exposed to irradiation (total body irradiation a portal irradiation) Included in the last factor is the inherent sensitivity of the exposed tissues (the spleen liver, and gastrointestinal tract being far more sensitive than an extremity receiving irradiation)

Some patients will develop nausea and a sense of ill feeling and may even vomit by simply being placed in the room containing the irradiation equipment Whether this is psychogenic or as has been suggested the effect of ozone in the atmosphere is problematic The treatment of such symptoms consists of merely giving the patient a mild sedative before the therapy commences

In other instances as the treatment progresses especially if therapy is given over the abdominal cavity an intensification of the symptoms of nausea and vomiting develops the patient may feel extremely weak become exhausted after the slightest exertion and develop headache and a sensation described as general sickness

The cause of these symptoms is not known They are believed to be due either to the effects of ionization radiation upon normal tissues with its aftermath of secondary ionization within the tissue and the institution of certain chemical reactions within the irradiated tissue or to effects secondary to destruction of the diseased tissue akin to a Herxheimer reaction In many instances the cause may be psychogenic Inasmuch as it is not known no specific therapy is available

Innumerable drugs have been advocated for treating systemic reactions (irradiation sickness) but none has proved entirely satisfactory A full list of such suggested medicaments could fill several pages and serve no useful purpose The more recently described preparations include antihistamines hormones (DOCA cortisone ACTH Adrenalin corpus

luteum) vitamins (thiamine hydrochloride ascorbic acid inositol choline chloride pyridoxine riboflavin nicotinic acid bioflavonoids liver extract and others), antibiotics (Aureomycin) certain amino acids (cysteine methionine and others), anoxia and every analgesic and sedative varying from simple aspirin to large doses of morphine

The symptoms may persist despite the use of any drug and may be so severe that treatment must be discontinued If the patient can tolerate the treatment for five days a week end rest may permit resumption of treatment the succeeding week If this regime can not be tolerated a reduction of the daily dose may be acceptable to the patient

The editors have found that the use of a mild sedative or one of the tranquilizing drugs such as meprobamate is sometimes effective If headache or dizziness is the major symptom such drugs as dimenhydrinate or parachloramine hydrochloride are efficacious in causing diminution or disappearance of the symptoms The use of chlorpromazine one half or an hour before therapy given intramuscularly in a rather large dose which varies between 50 and 100 mg has proved extremely effective *in many patients in either preventing or* decreasing the degree of bothersome symptoms from irradiation

As therapy continues the cumulative effect of daily dosages may produce such complications as hemorrhage due either to a thrombocytopenia or increase in capillary fragility or the production of a circulating anticoagulant Following extensive portal irradiation or subsequent to total body irradiation a pancytopenia may occur or anemia sometimes of severe degree may develop The actual causes of these alterations are not known but they probably represent the end result of severe destructive actions which include the actual destruction of the blood elements such as might occur following irradiation to the liver (a vascular sponge with large volumes of blood being exposed to the beams of ionizing radiation) the production of hemolysis with resultant hemolysis of blood elements damage to the reticuloendothelial system with blockage of the regeneration of certain blood elements and damage to the bone marrow or they may be due to actual hemorrhage

Total body irradiation may occur subsequent to so called spray therapy from a regular x ray therapy generator such as the now obsolete Heublein unit or from radioactive isotope therapy or exposure to an atomic blast

A careful review of the acute radiation syndrome was published in 1952 from the Los Alamos Scientific Laboratory and the Argonne National Laboratory based on personnel suffering accidental exposure on the Atomic Energy Program and supplemented by information gained at Hiroshima and Nagasaki [18] The reader is referred to this excellent review for further information on the induced changes and concepts of treating such exposure This subject is beyond the scope of this addendum

The combination of leukopenia and poor general nutrition of these patients contributes to increased susceptibility to infection and those exposed to overwhelming doses of radiation (such as occurs after exposure to an atomic bomb blast) practically always suffer from severe infection Malnutrition is a concomitant accompaniment because the symptoms prevent proper alimentation

Efforts to prevent or minimize the systemic *effects of irradiation have not been rewarding* at least as far as the human is concerned Jacobson and others have demonstrated that shielding the spleen from the radiation beam will exert a markedly beneficial protection from the systemic effects of irradiation Their experiments were performed on mice but the same situation does not prevail for the human The induction of anoxia has been described as a protection against the untoward effects of irradiation but its practical application to the human receiving radiation therapy has not proved feasible Such experimental procedures as transplanting bone marrow or splenic extract into irradiated animals have not proved effective in the treatment of systemic reactions in the human The use of cysteine as a protection against irradiation has been described in animals but its use in the human has not been particularly effective A host of other chemicals have been described for preventing the untoward and deleterious effects of irradiation as well as for controlling the ensuing symptoms These include adenosinetriphosphate flavonoids Aureomycin etc without too gratifying a result to the patient

Hormone Therapy, Chemotherapy, and General Care of the Cancer Patient

CHAPTER 31

The Biologic Effects of Hormones as They Apply to Cancer Treatment

Robert A Huseby

INTRODUCTION

Until comparatively recently cancer was considered as representing a completely autonomous growth That is except for the restrictions placed on it by the vasculature of the host cancerous growth was believed to be a law unto itself growing completely beyond the bounds of those mechanisms of the host that control normal growth processes and therefore growing without regard to the physiology or the anatomy of the host The demonstration that alterations in the hormone status of the host could in certain instances not only halt this relentless uncontrolled growth but even effect very significant decreases in the size of existing cancerous deposits certainly seems to dispel this theory of complete autonomy In its stead a newer concept has arisen that of the dependency of certain cancers opening an entirely new field for research Although to date relatively few types of cancers have been shown to be dependent and all of these through the demonstration of regressive responses to hormonal alterations it seems quite possible that in the future cancer dependency in other as yet undefined areas may be demonstrated so as to expand greatly the therapeutic usefulness of this newly recognized characteristic of malignant neoplasia

RELATIONSHIP OF HORMONES TO CARCINOGENESIS

Inasmuch as certain hormones are potent stimulators of normal growth processes it seems logical that they might also be related to the production of abnormal growth Actually before the concept of hormones was clearly defined the relationship of ovarian function to established breast cancer was investigated [7] and rather early in the study of animal neoplasms the relationship of ovarian function to mammary carcinogenesis in mice was established [20 59 64] With the isolation of pure estrogenic hormones it appeared that all that would be necessary to produce malignant neoplastic overgrowths of certain sexual tissues would be to subject them to prolonged hormone stimulation Lacassagne [57] by the injection of estrogenic hormones was able to produce mammary carcinomas in male mice which otherwise would not have developed such tumors As the investigation of this problem progressed however it soon became evident that although under certain circumstances cancer did develop as a result of endocrine alterations the relationship of hormone stimulation to malignant transformation was not a simple one The precise mechanisms of action of the hormones in carcinogenesis are still not understood [29 31]

Genetic Constitution and Neoplastic Formation

Certain facts have been established in animals although very little that applies to man has been elucidated [51 53 66 72] Factors other than the hormone alterations determine whether or not a treated animal develops a neoplasm One of the most important is the genetic constitution of the animal which not only determines whether or not a tumor appears but it also selects in large measure in which sexual tissue the neoplasm

develops Present data strongly suggest that there is no particular inheritance of an overall susceptibility to the development of cancer [12, 60] Rather certain characteristics seem to be inherited that make the development of a given type of tumor in a specific tissue likely Thus one strain of mice may be genetically susceptible to the development of interstitial cell tumors of the testes after prolonged estrogenization while in other strains with similar treatment a great number of mammary or pituitary tumors will result [31] It is certain that different species of animals metabolize hormones somewhat differently and such differences could be of importance in determining the end organ response It has also been demonstrated however, that the end organs themselves respond differently as far as the formation of tumors is concerned even when placed in the same environment [48] Thus when adrenals of donor mice from two different strains were placed in the identical environment of castrated and adrenalectomized hybrid mice the adrenals from one stock became cancerous while those from another remained essentially unchanged It is evident therefore that the genetic constitution of the animal can influence the hormone cancer relationship in at least two major ways altering the organism s metabolism of the various hormones and altering the response of the end organs to those hormones presented to them

Cocarcinogens and Hormone Cancer Relationship

In certain tumors in animals definite cocarcinogenic agents have been demonstrated This is best exemplified in mammary carcinogenesis in mice In all strains of mice so far studied with the apparent exception of the Heston C3H stock [42] three factors must be present before many cancers of the breast develop (1) the animals must be genetically susceptible to the development of breast cancer (2) their mammae must be subjected to a qualitatively and/or quantitatively adequate hormone stimulation and (3) the animals must be infected with a virus that is generally passed from mother to offspring in the milk during nursing [9 10] If any one of these three factors is lacking few spontaneous breast cancers result even though the other two factors are present It has been shown however, that mammary cancers can be produced in genetically susceptible mice lacking the milk agent either by the proper administration of hydrocarbon carcinogens [55] or by certain hormonal manipulations [62] In view of this latter finding it is interesting to note the very fragmentary data suggesting that the infection with the milk agent virus may alter hormone metabolism in cancer susceptible mice [11, 69] In addition, it has been shown that in genetically susceptible mice possessing the milk agent the tendency for virgin females to develop breast cancer is genetically controlled [11 13 41] and this inherited tendency is apparently mediated through the endocrine system

Other cofactors have been described Thus x rays and hormones may act together in the production of leukemia in mice [54] as may hydrocarbon carcinogens and hormones in the production of breast cancer in mice [55]

Metabolic Factors and Hormone Cancer Relationship

Most studies indicate that the period of carcinogenesis is relatively long in terms of the life span of the animal under investigation This fact has greatly hampered the investigation of the effects of exogenously supplied protein hormones upon carcinogenesis since in most instances *antihormones* are produced against the administered protein and its hormone action is relatively quickly negated Environmental factors are also of importance since not only do alterations in the *nutritional status* of the animal for instance alter the production of various hormones by the animal [46] but they also may alter the responsiveness of certain end organs to the trophic action of the hormones that are present [3 33 73] Finally the intricate interbalancing of the endocrine system makes interpretations of results difficult Thus although the administration of a given hormone may greatly alter the frequency of occurrence of a certain type of tumor in a group of experimental animals the pathway of action of the administered hormone may be a very circuitous one involving alterations in activity of one or more of the glands of

internal secretion and the altered function of these glands may in reality be responsible for the altered frequency of tumor development

POSSIBLE MECHANISMS OF ACTION OF HORMONES IN CANCER THERAPY

The consideration of how hormone alterations might result in a definite though temporary regression of certain established cancers is made difficult by the newness of the expanded interest in this field and therefore the paucity of fundamental data It is unfortunate furthermore that there are few tumors in experimental animals that lend themselves to investigation as far as the therapeutic effects of hormone alterations are concerned There are no frequently occurring or easily induced prostatic carcinomas available for study in laboratory animals and mammary carcinomas in mice are not significantly altered either by ovariectomy or by the administration of estrogen [49 61] although their growth rate may be retarded in certain instances by the administration of androgens [26]

Prostatic Cancer

The situation that obtains in the human with regard to the response of established prostatic cancer to hormone alterations appears at least on the surface to be the most simple to consider There seems to be little doubt from the work of Huggins and Hodges [44] that not only normal but also cancerous prostatic tissue is stimulated probably both as far as its functional and its proliferative aspects are concerned by the administration of testosterone propionate Since in a high percentage of cases orchiectomy is rather promptly followed by a diminution in tumor size and function (as indicated by a reduction in the serum acid phosphatase) it would appear that the malignant neoplasm requires a continuing stimulation from a trophic hormone for continued and uninterrupted growth This situation seems to be closely analogous to that seen in certain estrogen induced interstitial cell tumors of the testes in mice [30] These tumors once they develop in male mice that have received estrogen parenterally for relatively prolonged periods will metastasize to the regional lymph nodes and thus the tumors as they exist in primary host fulfill the criteria of malignancy If however bits of tumor tissue are transplanted to other individuals of the same genetic strain the transplanted tumor tissue will grow only in estrogenized animals It would appear then that the tumor cells themselves have not become sufficiently autonomous to continue their disorderly growth without the continuance of some stimulating factor possibly of pituitary origin that is present in estrogenized male and female mice The work of Deming with human prostatic cancer seems to add weight to the analogy When bits of human prostatic cancer were transplanted to the anterior chamber of the guinea pig s eye the tissue was found to grow in many of the male animals but in none of the females This phenomenon held for the first seven serial transfers of the carcinomatous tissue but from the eighth transfer generation on the tumors were found to grow in either female or male recipients Also during the early transfers of the tumor no growth was noted in castrate male recipients It would appear that this human cancer tissue originally required a stimulus from functioning testes or injected testosterone for its growth in the anterior chamber of the guinea pig s eye but with successive transfers it became sufficiently autonomous to grow in the absence of demonstrable hormonal stimulation

Whether the regrowth of prostatic cancer in men successfully treated by castration and/or estrogenization occurs because of an increase in autonomy of the cancer cells or because of an increased production of androgens by extragonadal tissues presumably the adrenal cortex has not been adequately evaluated at the present time Following the lead of Huggins and co workers [43] a fair number of castrate patients with reactivated prostatic cancer have been adrenalectomized and maintained on cortisone [75] Although the 17 ketosteroid output in the urine is routinely reduced by this procedure the clinical response of the patients has been variable Significant although rather short lived subjective improvement frequently follows this procedure and in some patients so treated definite objectively measurable regressions in tumor size are noted but prolonged and dramatic

regressions seem to be the exception rather than the rule

The basis for action of additive hormone therapy in prostatic cancer however awaits elucidation It has been assumed with considerable justification that the administration of relatively large doses of estrogen are effective in causing the regression of prostatic cancer by bringing about an endocrine castration that results from suppression of pituitary gonadotropin causing in turn a decreased androgen production by the testes and adrenals This thesis is strengthened by a decreased 17 ketosteroid excretion in prostatic cancer patients receiving diethylstilbestrol [21] Whether this type of castration is complete or whether the estrogenic hormones themselves may partially neutralize the effect of residual circulating androgen is not clear Furthermore a second regression in the case of reactivated prostatic cancer may follow administration of testosterone [14 63] of progesterone [36 74] or of massive doses of estrogen [40] In addition the administration of testosterone to patients who have not previously received hormone therapy is by no means always followed by a worsening of their cancer [74] Such observations raise the question as to whether the relationship of prostatic cancer to testicular function is indeed as simple as outlined previously

Breast Cancer

The over all picture of breast cancer and its response to hormone alteration appears more complex than that encountered in prostatic cancer As far as one can judge at present the relationship of oophorectomy to the induction of regressive changes in established human breast cancer appears analogous to that of orchiectomy and prostatic cancer i e interruption of ovarian function removes the major source of the estrogenic hormones upon which certain breast cancers are dependent for their continued and uninterrupted growth The administration of relatively large quantities of androgenic substances might also be regarded as an endocrine castration since it routinely leads to a cessation of the menses excretion of gonadotropins in the urine is reduced [68] However the fact that androgen administration to the postmenopausal woman seems to be as effective if not somewhat more effective than it is to the premenopausal woman strongly suggests that some other mechanism is also functioning Although it is possible that the administration of androgens to the postmenopausal woman might be effective through the suppression of some extragonadal production of estrogen other endocrine changes [25, 65 70] suggest certain different modes of action

In the experimental work that led Haddow and associates [4 37 38] to administer estrogens to patients with advanced breast cancer certain hydrocarbon carcinogens that are initially growth inhibitors were found to impede the growth of transplanted tumors in rats Since Zondek [77] had found that the growth rate of rodents was markedly inhibited by the administration of large doses of estrogen these substances were tested for their inhibitory effect on the growth of transplanted tumors and they were found to be somewhat effective Throughout this experimental work the hydrocarbon carcinogens and later the estrogens in large doses were considered to be rather general growth inhibitors with at least a portion of their growth inhibiting action being mediated through a suppression of pituitary function [39] Two problems need then to be considered first is pituitary function necessary for the growth of cancerous tissue and secondly in the doses used in the treatment of human breast cancer are the estrogens acting as general growth inhibitors or is their tumor inhibiting effect more specific in nature?

Experiments have shown that cancerous tissue can grow in the complete absence of hypophyseal stimulation [5 6 28 62 68 71] The rate of tumor growth is reduced in such animals As far as can be determined there have been no instances recorded in which a regression of an established malignant tumor has occurred following hypophysectomy in experimental animals Although it is difficult to maintain hypophysectomized animals long enough to produce tumors in them experimentally a few papillomas of the skin were observed in hypophysectomized mice following the topical application of 3 4 benzpyrene [56] and subsequently it has been reported that hypophysectomized mice develop lymphoid tumors following exposure to ionizing

radiation as readily as do intact irradiated control animals [64a]

More recently experience with the therapeutic effectiveness of total ablation of the pituitary and adrenal glands has accumulated so that at present there is little doubt that significant regression of tumor deposits can be effected by either means in women who have previously been castrated Whether or not the mechanism by which these procedures produce their effect is the same has however not yet been answered It might well be that both are effective by decreasing substantially the extragonadal production of estrogen adrenalectomy by removing a gland producing estrogen hypophysectomy by removing the stimulatory hormone responsible for the extragonadal elaboration of these hormones In addition the removal of the pituitary could be effective by removing the source of growth hormone and/or prolactin which might be influential in augmenting tumor growth although these latter possibilities have as yet not been proved It should be pointed out that in younger women where it can be tested both procedures are effective almost entirely if not exclusively in those cases in which tumor deposits had previously regressed in response to the interruption of ovarian function This would suggest that it is only those cancers that are more or less dependent on estrogen that regress following adrenal or pituitary ablation This does not of necessity mean however that the only effect of either or both of these procedures is to decrease the extragonadal production of estrogen but may only indicate that the cancers that did not respond initially to estrogen removal are for all intents and purposes autonomous and will not respond to any hormonal alteration

Administration of estrogenic hormones at the dose levels employed in the therapy of breast cancer does suppress the production and/or release of certain pituitary hormones particularly the gonadotropic hormones Whether or not a significant suppression of the production of growth hormone results as suggested by Zondek [78] or whether a situation similar to the mammary gland stunting effect of large doses of estrogen as described in animals [27 32] obtains in these patients is unknown In a study of the response of the normal breast tissues of postmenopausal patients with advanced breast cancer who were receiving estrogen therapy [50] it was found that usually the normal breast epithelium increases in amount during the first few months of estrogen administration Surprisingly in the majority of breasts studied rather normal appearing lobules were encountered and in a few of the breasts large lobules similar to those seen in pregnancy were found In addition proliferation of the fibroblastic stroma of the breast was encountered There was not any direct correlation between the magnitude of these various changes in the normal breast tissues and the response of the tumor to therapy It would appear then that in the dosages employed in the therapy of human breast cancer estrogens are not acting as general growth inhibitors and the mammary gland stunting effect of large doses of estrogen described in several species of animals is not operating This of course does not mean that a lesser degree of pituitary inhibition may not be an important factor in causing the regression of established breast cancer However to date there is no evidence to support such a thesis Since the normal epithelium of the breast is apparently proliferating at the same time that the cancerous breast epithelium is undergoing regression the growth inhibiting effects of the estrogens would appear to be rather specific for the neoplastic tissue

Another mechanism by which the administration of estrogenic hormones to elderly women might cause the regression of an established breast cancer is by augmenting the host s resistance to the growth of the tumor It must be admitted that such a consideration is hypothetical at present since there is very little concrete evidence for the existence of an active host resistance to the growth of breast cancer There are certain suggestions that such a resistance might exist such as the desmoplastic reaction frequently elicited by breast cancers and the long latent period often seen between cancer embolization and the formation of an actively growing tumor There is however no information concerning the nature of any such resisting force It seems possible that hormones might affect tumor growth by improving the general status of the surrounding normal tissue Estrogens and andro-

gens play a role in the maintenance of normal body structure [2] and in the maintenance and/or development of certain connective tissues of nonsexual organs [15]

Preliminary investigations aimed at the problem particularly as regards estrogen therapy and breast cancer have been undertaken The suggestion has been made that there

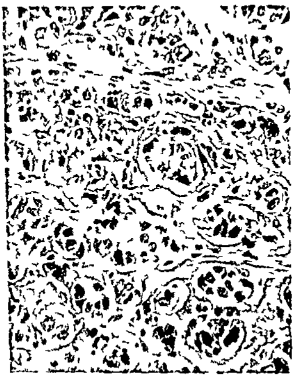


Fig 31 1 A typical region of a breast cancer metastatic to the dermis of a seventy seven year-old woman *prior to* administering estrogen therapy There was no histologic evidence of desmoplasia and stains *for alkaline* phosphatase were negative (× 375) (*From* Robert A *Huseby* *Estrogen Therapy in the Management of Advanced Breast Cancer* *courtesy The American Surgeon*)

might occur an active fibroblastic proliferation about the tumor as it regresses [1] However investigations carried out in our laboratory have failed to support this observation Contrariwise in two instances where the supporting collagenous connective tissue of the metastatic deposit showed active fibroblastic proliferation prior to the administration of estrogen all signs of fibroblastic activity disappeared as the tumor underwent regression Large deposits of breast cancer may regress completely with no residuum of connective tissue as would be expected if the tumor regression was effected by a *proliferation of the connective tissue* surrounding the tumor cells *Although* removal of partially regressed tumor masses frequently reveals a connective tissue capsule about the tumor and/or relatively large amounts of collagenous connective tissue within the tumor in such specimens the connective tissue is composed of heavy collagen bundles with relatively few adult fibro-

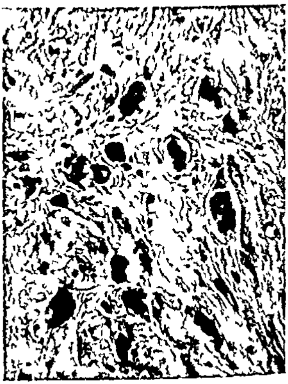


Fig 31 2 A typical region from the same tumor illustrated in Figure 31 1 after the patient had ingested 3 mg of ethinyl estradiol for four weeks The tumor had reduced considerably Although the connective tissue has increased relatively in amount there is neither histologic nor histochemical evidence of fibroblastic proliferation and the apparent increase seems most likely due to the disappearance of tumor cells There is very little desmoplastic reaction about the tumor cells which have been altered morphologically by the therapy (× 375) (*From* Robert A Huseby *Estrogen Therapy in the Management of Advanced Breast Cancer* courtesy *The American Surgeon*)

cytes interspersed throughout This suggests that the increase in connective tissue might be relative resulting from the decrease in the quantity of cancerous epithelium (Figures 31 1 2 3 4 5) The entire problem of carcinoma connective tissue relationship and how it is affected by endocrine alterations awaits further elucidation

Whether or not cancerous tissues differ antigenically from the normal tissues of the

host in which they arose has been investigated extensively in experimental animals It has been shown that animals can be immunized against the proteins of tumors that originally appeared in animals genetically dissimilar from those that receive the transplant and that such immunization can inhibit or completely prevent the growth of such tumor transplants as would otherwise grow and kill the recipient [76] It has also been demonstrated that the estrogenization of mice may enhance the protection afforded by such immunization [67] Whether a similar mechanism might be functioning in the case of estrogen therapy in spontaneous breast cancer in human beings is doubtful To my knowledge it has as yet not been possible successfully to immunize mice against mammary tumors that originally developed in animals genetically identical to those receiving the tumor transplants [8 35] There is some evidence that immunity may be developed against chemically induced sarcomas arising in inbred animals [34] but certainly in the great majority of experiments successful immunization has been produced only where the tumors employed for transplantation arose in animals that were genetically dissimilar to those receiving the grafts

It has also been suggested that the administration of estrogen to elderly women with breast cancer is effective treatment in that it rebalances an existing hormone imbalance This is an interesting hypothesis but proof is lacking Furthermore breast cancers that originally developed in regularly menstruating women in whom there was a "normal" estrogen supply are also responsive to estrogen therapy if the patient has passed through her menopause five or more years prior to the appearance of the recurrence of the carcinoma It appears a bit difficult to

Fig 31-3 A section from the same tumor illustrated in Figures 31 1 and 31 2 four months after commencing estrogen therapy During treatment the neoplasm had disappeared completely on clinical examination This small cluster of cells represents the only tumor identified in many sections The remainder of the excised tissue showed normal nonproliferating dermal connective tissue The connective tissue in two biopsies performed after estrogen therapy was negative for stainable alkaline phosphatase except in the capillaries (× 375) (From Robert A. Huseby Estrogen Therapy in the Management of Advanced Breast Cancer courtesy The American Surgeon)

Fig 31-4 A typical region of a breast cancer metastatic to the supraclavicular lymph nodes of a sixty nine-year-old woman prior to the institution of estrogen therapy There is considerable desmoplasia about clumps of tumor cells indicated by many fibroblasts with large leptochromatic nuclei which present an intense staining reaction for alkaline phosphatase (× 175)

apply the concept of rebalancing a hormone imbalance to this situation since, at least as far as estrogen is concerned, the "balancing" has tended to re-establish the situation in which the cancer originally developed.

It would appear then that although some rational explanation, though probably incomplete and not necessarily correct, can be set forth to cover the response of prostatic cancer

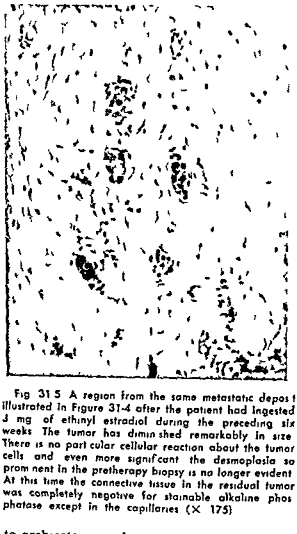


Fig 31 5 A region from the same metastatic deposit illustrated in Figure 31-4 after the patient had ingested 3 mg of ethinyl estradiol during the preceding six weeks. The tumor has diminished remarkably in size. There is no particular cellular reaction about the tumor cells and, even more significant, the desmoplasia so prominent in the pretherapy biopsy is no longer evident. At this time the connective tissue in the residual tumor was completely negative for stainable alkaline phosphatase except in the capillaries (× 175)

to orchiectomy and even to estrogen administration and of breast cancer to oophorectomy and possibly to androgen administration, the mechanism by which estrogen administration to the postmenopausal woman effects a regression of certain breast cancers remains entirely obscure and puzzling. This is true also of the mechanism by which orchiectomy or the administration of estrogens effects a regression of cancer of the male breast. It is also very difficult to explain why certain deposits of metastatic breast cancer will respond dramatically to a given endocrine alteration while other deposits in the same patient appear to be entirely unaffected. It is not uncommon in an elderly patient receiving estrogen to have the metastases in the soft tissues regress completely while those in the bony skeleton progress at approximately the same rate as they did prior to the administration of the hormone. This happens so frequently that any proposed mechanism of estrogen action must necessarily take into consideration the tissue surrounding the cancer cells as well as the cancer cells themselves. Somewhat more perplexing is the situation noted most frequently in testosterone therapy, that of having certain metastases in the bony skeleton regress with a filling in of the bony defect while metastases in other regions of the bony skeleton continue to progress.

The reactivation of cancer growth in the face of a continuance of the hormone therapy that brought about the initial regression and the response of these reactivated cancer deposits to further endocrine alterations present challenging problems. Although the problem is at present very perplexing, it may ultimately prove to be an important key in the search for the mechanisms involved in hormone therapy. Several possibilities present themselves. As with the human prostatic cancer transplanted to the eye of the guinea pig, it seems possible that cancer cells that originally required hormonal stimulation for continued growth might in time become autonomous. On the other hand, reactivation might occur as a result of a changed hormone metabolism of or hormone production by, the host that harbors the cancer. Thus extragonadal tissues might at least partially assume the production of the trophic hormone involved or, where the therapy consists of the administration of a hormone, the host might alter its metabolism of that hormone so that the inhibitory effects once produced are no longer evident.

The situation, particularly as it obtains in breast cancer that has regressed in response to the administration of estrogen, appears to be rather more complex. Frequently, if a breast cancer reactivates in the face of continued estrogen therapy, the discontinuance of the estrogen brings about a second and often dramatic regression of the tumor. This second

regression may last for several months and when the cancer reassumes its growth the administration of estrogen may be followed by a third period of tumor regression Since the administration of exogenous estrogen to premenopausal women or to women during their menopause not infrequently results in acceleration in the growth of breast cancer one wonders if even in elderly women some impetus to cancer growth may not result from estrogen administration If such is the case the initial tumor regression results because the growth stimulus is more than overcome by the enhanced inhibiting forces brought into play by the administered hormone As therapy continues however these inhibiting forces may lessen in intensity possibly owing to an alteration in the host s metabolism of the estrogen so that eventually the tendency for the tumor to proliferate again breaks through With the discontinuance of the estrogen and its associated trophic effect a second regression then occurs During the period of no therapy the hormone metabolic pattern of the host may again return to its pretherapy status so that a second course of estrogen administration may again be effective In order to make any such a thesis at all tenable it must be assumed that the inhibitory forces are maintained for a period of time after the discontinuance of the hormone while the trophic effects of the hormone rapidly disappear The second portion of this assumption is in accord with the rapid diminution in pain often seen following oophorectomy in young patients with bony metastases from breast cancer The other premises upon which this thesis is based have not been adequately investigated although changes in two enzyme systems one of which appears to be involved in steroid metabolism have been described in patients with continuing estrogen therapy [16 17] The possibility that the administration of a given hormone may change more than one aspect of the cancer host relationship should be seriously studied

It has also been postulated by several authors that cancer tissue may change so that a hormone that at first depressed tumor growth can later act as a trophic hormone that stimulates the growth of that tumor To state this in other terms in the face of a continued supply of a given hormone tumor cells may become dependent upon that hormone for their continued growth

Hormones and Thyroid Cancer

In addition to cancers involving the sexual epithelia two other malignant neoplasms are affected by changes in the endocrine environment Certain *thyroid carcinomas* retain functional capacities to concentrate appreciable quantities of iodine and to produce thyroxine In other instances the tumor tissue functions very little but after the host has been thyroidectomized the increased levels of pituitary thyrotropic hormones that circulate tend to increase the ability of the carcinomatous tissue to concentrate significant quantities of iodine and thus make them amenable to attack by the administration of radioactive iodine This is another example of cancerous tissue retaining a portion of the functional potentialities of the tissue of origin and responding to the same trophic hormone that regulates the function of the normal tissue

Response of Lymphomas to Certain Hormones

The rapid regression of certain *lymphoblastic tumors* following the administration of adrenocortical hormones might be another example of the same type of thing Certain of the adrenocortical steroids cause a very rapid lysis of normal lymphocytes [23 24] and certainly the effects of these steroids on lymphoblastic tumors are in many ways similar to those seen in the normal situation Since second responses to therapy are often slight as compared with the initial response it appears possible that those abnormal lymphocytes that retain more of the ability to respond normally to the action of cortical hormones had been lysed completely during the initial course of therapy leaving the more abnormal cell forms to reform the tumor masses

CHAPTER 32

Clinical Application of Hormones in Cancer Therapy

Julian B Herrmann

INTRODUCTION

The beginnings of endocrine therapy for carcinoma date back over half a century when Sir George Beatson stated that 'we must look in the female to the ovaries as the seat of the exciting cause of carcinoma, certainly in the mamma, in all probability of the female organs generally Beatson reported regression of carcinoma of the breast in women after removal of the ovaries however, apparently no efforts were made to investigate the nature of this influence and for the most part this palliative procedure failed to find acceptance About twenty years later interest was stimulated in the possible influence of the ovary on breast carcinoma by the investigations of Lathrop and Loeb they found that early ovariectomy reduced the frequency of spontaneous mammary carcinoma in certain strains of mice

The isolation of estrogen in 1923 [3] and the subsequent demonstration by Lacassagne [79] that the injection of this substance could induce mammary carcinoma in certain strains of male mice stimulated further study of ovarian relationship to breast carcinoma Estrogenic stimulation as a possible factor in the development of human breast and endometrial carcinoma has been suggested but not substantiated [4 5 21 40 104 135] It has however been established that castration the withdrawal of hormones can influence certain carcinomas in men and women

About the time that Beatson noted the influence of ovariectomy on carcinoma of the breast White in this country reported the effects of bilateral orchiectomy on prostatic hypertrophy (prostatic adenoma) he found that castration induced atrophy of the prostate After the isolation of androgenic substance in 1927 [25 94], Lacassagne and Raynaud demonstrated the influence of androgen on the generative organs of animals by injecting this hormone into the seminal vesicle of the rat and stimulating the growth of the seminal vesicle epithelium Subsequently, Huggins indicated the possible relationship of testosterone to human prostatic carcinoma he demonstrated that orchiectomy could produce effects on metastatic prostatic carcinoma comparable to those of ovariectomy on metastatic mammary carcinoma [70]

The first physiologic substances known to influence neoplasia are the hormones It is of interest and perhaps of significance that the neoplasms found to be sensitive to hormonal influence have their origin in the male and female generative system and related organs and in the lymphatic and hematopoietic systems

ENDOCRINE PHYSIOLOGY

The endocrine glands through their hormones serve as a regulatory mechanism for various physiologic functions Should this mechanism be disturbed structural and functional changes can be produced these may be modified or reversed by suppressing or augmenting the naturally occurring hormones Certain aspects of endocrine physiology and their relationship to hormonal therapy of neoplasia will be briefly discussed

Production and Release of Hormones

The hypophysis and hypothalamus considered the regulatory center of the endocrine

system are believed to exercise regulatory control by means of hypophyseal trophic hormones carried by the circulation to target glands such as the gonads and the adrenal cortex These target glands stimulated by the appropriate trophic hormones produce and release characteristic hormones that are transported by the circulation to the organ or tissue upon which they produce their effects It is believed that some of these hormonal secretions in the blood are carried in the free form

gonadotropic The adrenocorticotropic hormone (ACTH) stimulates the production of adrenocortical steroids The production and release of the gonadal steroids are stimulated by the following gonadotropic hormones luteinizing hormone (LH) also known as interstitial cell stimulating hormone (ICSH) controls the formation of the ovarian corpus luteum and the secretion of progesterone and is believed to control the production of testosterone by the Leydig cells of the testis luteo

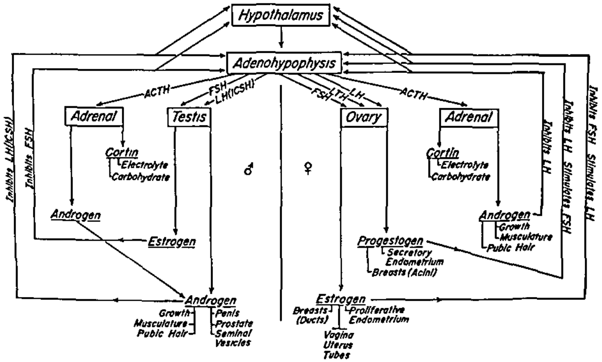


Fig 32 1 Gonadotropic hormonal relationships

but that about 75 per cent are combined with plasma protein to prevent loss through the kidney

Nature of Hormones

The hypophyseal trophic hormones appear to be proteins or polypeptides and have a large complex molecule The gonadal and adrenal cortical hormones are steroids compounds with a chemical structure similar to cholesterol bile acids ergosterol (vitamin D) as well as to certain carcinogenic substances

Hypophyseal Trophic Hormones

There are two groups of trophic hormones concerned with the production and release of steroid hormones adrenocorticotropic and

tropic hormone (prolactin) stimulates the corpus luteum to secrete progesterone and also is the secretory hormone of the mammary gland follicle stimulating hormone (FSH) activates the ovarian follicles and in conjunction with the luteinizing hormone governs the production of estrogen in the ovarian Graafian follicles Somatotropin is a growth stimulating hormone and has no direct effect on the production of gonadal hormones

Gonadal and Adrenal Steroid Hormones

The gonadal hormones whose major function is to effect maturation of the reproductive organs and to maintain their differentiation appear to be among the most potent hormones to influence certain neoplastic diseases of the

sex organs Hormones gonadomimetic in character which originate in the adrenal cortex appear also to influence neoplasms

Testosterone, presumably secreted by the interstitial cells (Leydig cells) of the testis is considered one of the precursors of the other naturally occurring androgenic substances among which androsterone isoandrosterone, and etiocholanolone are some of the more important

Estrogen is secreted by cells of the ovary follicular thecal granulosal, luteal and possibly by the ovarian cortical stroma The naturally occurring estrogen is estradiol and two of its more important derivatives are estrone and estriol

Androgenic and estrogenic substances can be obtained from the adrenal cortex in men and in women and the adrenal cortex is the chief source of androgenic hormone in women The more important steroids from a clinical point of view that have been isolated from the adrenal cortex are cortisone 17 hydroxycorticosterone (hydrocortisone) desoxycorticosterone and aldosterone

Small amounts of androgen are believed to be produced in the stromal elements of the ovary [123] and small amounts of estrogen by the Sertoli cells of the testis

Progesterone is produced chiefly by the corpus luteum of the ovary and in small amounts by the testis and the adrenal cortex

Release of Hormones from Target Glands

The mechanism of release of these hormones from the target glands has not been determined It is supposed that the trophic hormones of the hypophysis alter the permeability of the cells of the target glands or produce a change in the physical characteristics of the intracellular substances that results in the release of the hormones

Regulatory Mechanism of Hormone Secretion

The hypothalamus is considered to influence directly the production of adenohypophyseal trophic hormones by means of humoral agents originating in the hypothalamic fibers these agents are transmitted to the hypophysis by way of the hypophyseal portal vessels and the output of hypophyseal trophic hormones is controlled by a physiologic mechanism According to this concept high blood concentrations of the hormones secreted by the target glands such as the gonads and the adrenals depress the secretion of hypophyseal trophic hormones that in turn regulate the hormonal output of these target glands low concentrations in the blood effect an increased secretion of the appropriate trophic substances by the adenohypophysis There is evidence that a neural as well as a hormonal mechanism is involved in the regulatory process

Androgenic and estrogenic hormones are secreted by each sex possibly because of the common embryologic origin of the testis and the ovary It is believed that a state of equilibrium is maintained by a relatively constant rate of hormonal secretion by the endocrine glands that changes in equilibrium take place in accordance with varying needs of the organism and that when these needs are supplied homeostasis is re-established The complexities of this mechanism are not too well understood Hormonal equilibrium can be influenced by unphysiologic measures of augmentation or withdrawal of hormones The administration of large amounts of estrogen or androgen decreases the production and release of gonadotropins adrenocorticotropins and prolactin by the hypophysis Withdrawal of hormones (castration) lowers the circulating gonadal hormonal titer may induce enlargement of the hypophysis and increases the production and release of gonadotropins After castration a decrease of urinary estrogenic and androgenic substances in men and in women may be observed Subsequently substantial amounts of these products may continue to be excreted however and may be recovered from the urine of either sex

The Influence of Nutrition on Production, Inactivation, and Excretion of Hormones

PRODUCTION AND ACTIVATION OF HORMONES

An adequate state of nutrition is necessary for the production activation inactivation and excretion of hormones Despite an otherwise adequate diet the lack of sufficient quantities of particular food elements vitamins growth factors chemical substances and min

eral elements can interefere with the production action inactivation and excretion of hormones A low protein diet can effect suppression of adenohypophyseal secretion in rats and in humans For the proper functioning of the adrenal glands vitamins such as ascorbic acid thiamin riboflavin and pantothenic acid are necessary Acute pantothenate deficiency in rats can induce adrenal hemorrhage and necrosis this can be counteracted by the administration of pantothenate there is evidence that the adrenal is unable to elaborate hormones during the period of pantothenate deficiency [95]

An adequate amount of vitamin E is essential to obtain full androgenic effect on the comb of the capon To induce characteristic estrogen effects on the oviduct of the chick folic acid in sufficient quantity must be present [12 64]

Starvation can decrease the production of hormones and also can decrease the ability of the liver to inactivate them (see below) War prisoners on a starvation diet developed bilateral gynecomastia when released from prison and provided with an adequate diet [75] An explanation for this phenomenon was that both estrogen production and hepatic function were depressed by inadequate diet that when an adequate diet was supplied hormone production outstripped hepatic function recovery so that inactivation of estrogen by the liver was delayed resulting in gynecomastia

INACTIVATION AND EXCRETION OF HORMONES

The function of organs other than the liver in the intermediate metabolism of the steroid hormones is not as yet understood It has been suggested that the kidney may participate in the metabolism of the steroid hormones and that the blood may contain an enzyme that oxidizes estrogen to a biologically inert substance It has also been suggested that estrogen which circulates probably as a protein or glucuronide complex is removed from the blood by the hepatic cells and is there converted into a substance of little or no estrogenic activity possibly by an enzyme to which the name of estrinase has been given after temporary storage in the liver the substance is reactivated and excreted into the bile with which it enters the duodenum it is then reabsorbed and again passes through the liver undergoing an enterohepatic circulation similar to that of the bile acids ultimately it is converted into a permanently inactive substance that is excreted in the urine as a sulfate or glucuronidate conjugate or is gradually destroyed [14 15] It is supposed that progesterone is converted to pregnanediol in the liver conjugated with glucuronic acid and in this form is excreted in the urine There is evidence that androgen is inactivated in the liver and that some is converted in the body into an estrogenic substance probably estrone

An adequately functioning liver is a prerequisite for inactivation of steroid hormones Some experimental evidence indicates that a vitamin B complex deficiency in rats decreases the capacity of the liver to inactivate estrogen [10] This may be due to liver damage resulting from decreased protein intake associated with vitamin deficient diets A cirrhotic liver unable to inactivate estrogen may induce persistently high blood levels of the hormone and may cause testicular atrophy gynecomastia or both

It is believed that about two thirds of the urinary androgenic substances and some of the estrogens in men and all the urinary androgenic substances and some of the estrogens in women are derived from products elaborated by the adrenal cortex [15 81 107, 118] These metabolites of adrenal cortical substances belong as do the metabolites of testosterone to the group of 17 ketosteroids [91] There are significant qualitative and quantitative changes in the excretion pattern of 17 ketosteroids in certain patients with neoplastic conditions [27] and certain neoplasms of the gonads and adrenal cortex are associated with high excretion levels of 17 ketosteroids (Table 32 1)

MECHANISM OF SEX HORMONE ACTION ON TARGET ORGANS AND TISSUES

Growth maturation and functional activity of mammalian reproductive organs are influenced by appropriate sex hormones Endogenous or exogenous sex hormone stimulation induces at first an imbibition of water and electrolytes by the tissues of the generative

TABLE 32 1 —SUMMARY OF ANDROGENS AND 17 KETOSTEROIDS IN HUMAN URINE*

Males			*Females*		
	Per cent of normal adult male level			*Per cent of normal adult female level*	
Status	*Andro gens*	*17 Keto steroids*	*Status*	*Andro gens*	*17 Keto-steroids*
Boys 5 yr	3	5	Girls 5 yr	5	5
10 yr	10	10	10 yr	10	10
14 yr	20	50	14 yr	25	60
Old men	15	30	Old women	25	
Eunuchoid	40		Eunuchoid	33	
Castrate men	40		Ovariectomized women	50	100
Addison's disease	50	38	Addison's disease	70	36
Pituitary insufficiency	3	5–10	Pituitary insufficiency		10
			Cushing's syndrome	40	163
Hyperthyroidism	50	80	Hyperthyroidism	10	60
Myxedema		57	Myxedema		16
Interstitial cell tumor of testis		10 000	Chorioepithelioma		100
Seminoma		150	Hydatiform mole		100
Teratoma testis		133	Hirsutism without tumor	100	200
Macrogenitalism (Prepuberal boys)		100			
			Adrenal cancer	Up to 4 000	Up to 20 000

* This table is a summary of the concentrations of androgens and 17 ketosteroids in the urines of normal and diseased humans The table illustrates relative magnitudes rather than a strict range of concentrations of these substances in the various conditions

From R I Dorfman *in* G Pincus and K V Thimann eds *The Hormones Physiology Chemistry and Applications* New York Academic Press Inc 1948 Vol 1 p 515

organs There is subsequent true growth of these tissues evidenced by mitosis and increase in their dry weight by an attendant increase in deposition of protein and glycogen in the tissues and by an increase in tissue metabolism with resultant increase in fibroblasts collagen and smooth muscle

Growth of specific tissues such as the prostate and the seminal vesicle subsequent to androgen stimulation and the growth of the breast and uterus subsequent to estrogen stimulation are general effects shared by the entire body but most marked in the generative organs This is due to an increase in nitrogen retention by the organism and an increase in the vascularity of the organs rather than to specific hormonal stimulation of the tissues involved There is a more marked general anabolic effect induced by androgen than by estrogen

The maturation effect of the gonadal hormones is specific for the sex organs but this specificity is independent of the individual's sex Estrogen can stimulate the development of breast tissue in the male and androgen can stimulate maturation of the rudimentary prostate in certain female animals

INHIBITION AND SYNERGISM OF HORMONES

There is evidence that the action of one hormone upon a given somatic tissue can in

fluence the effect of another hormone the administration of androgen can inhibit the estrus cycle in mice and the stimulating effect of androgen on the growth of the capon s comb can be retarded by concurrent estrogen administration [12]

Synergism also is important in hormonal interrelationships The characteristic influence of one hormone upon an end organ may not be obtained unless another hormone is administered to prepare the organ endometrial changes characteristic of progesterone stimulation are difficult to induce without preliminary preparation of the endometrium by estrogenic substances [12] The luteinizing hormone (LH) synergizes with the follicle stimulating hormone (FSH) to produce estradiol and ovulation In hypophysectomized rats the luteinizing hormone and the follicle stimulating hormone must be administered in the proper proportions to induce ovulation [12 111] To effect proliferation of the mammary gland luteotropin synergizes with estrogen [12]

GENERAL PRINCIPLES OF ENDOCRINE THERAPY FOR NEOPLASTIC DISEASES

In principle endocrine therapy for neoplasia is an attempt to change the tumor host relationship by altering the existing hormonal equilibrium This therapy should be employed only for patients with inoperable recurrent or metastatic neoplasms

Methods of Altering Hormonal Interrelationships Employed in the Treatment of Neoplastic Diseases

CASTRATION

The oldest method for altering existing hormonal interrelationships castration removes the site of origin of gonadal hormones Schinzinger in the latter part of the nineteenth century was the first to suggest the relationship between ovarian function and breast carcinoma [119] a few years later Beatson reported the favorable response induced by oophorectomy in a small group of women with advanced carcinoma of the breast After the discovery of the roentgen ray in 1895 roentgen castration was performed as a palliative procedure for carcinoma of the breast [ ] More recently orchiectomy was introduced as a therapeutic measure for advanced carcinoma of the male breast and of the prostate Castration is an established and important measure of palliation for advanced carcinoma of the breast in women and for carcinoma of the breast and of the prostate in men [52 62 70 128]

ESTROGEN

Estrogen was isolated from ovarian tissue by Allen and Doisy in 1923 [3] and its carcinogenic property in tests on animals was subsequently established The important observation of Haddow and his group that certain synthetic carcinogenic hydrocarbons with estrogenic activity could retard growth of malignant tissue suggested to them the trial of these substances [6 50] They obtained regression of tumors in some women with advanced carcinoma of the breast The estrogenic hormones have now become important agents in the palliative management of advanced breast and prostatic carcinoma [58, 98]

PROGESTERONE

The active principle of progesterone was extracted from the corpus luteum of the ovary by Corner and Allen in 1929 Since this hormone antagonizes or inhibits estrogen activity its use as a possible therapeutic agent in advanced breast and endometrial carcinoma has been investigated

ANDROGEN

Androgen was extracted from animal testes in 1928 and seven years later pure testosterone was synthesized [25] In 1939 Loeser and Ulrich independently suggested the possible therapeutic usefulness of this hormone The value of androgen as a therapeutic agent subsequently was established [1 59] when regression of cancer in women with advanced breast carcinoma was obtained by the administration over relatively long time intervals of relatively large amounts of testosterone propionate *

* Editorial Note The utilization of proper [illegible] Herrmann [illegible] in treating [illegible] carcinoma Th[illegible] originally [illegible] by Herrmann et al in 1946 [illegible]

ADRENOCORTICOTROPIC HORMONE AND CORTISONE

Dougherty and White in 1943 demonstrated that adrenocorticotropic hormone (ACTH) decreased lymphoid tissue in mice Subsequent clinical investigation indicated that cortisone as well as ACTH induced temporary regression of certain lymphomatous lesions and symptomatic improvement of the patient Acute leukemia lymphatic leukemia lymphosarcoma Hodgkin s disease and multiple myeloma may respond favorably to ACTH and cortisone therapy [32 131]

Inhibition of hypophyseal ACTH secretion may be induced by the administration of cortisone, depression of ACTH secretion diminishes estrogen and androgen secretion of the adrenal cortex thus cortisone administration may produce the same effect as adrenalectomy on mammary carcinoma and its host in some instances

ADRENALECTOMY

Gonadal adrenal and mammary gland interrelationships have been demonstrated in certain strains of mice [37 140] In this species

TABLE 32 2 —The Various Methods by Which Altered Hormonal Relationships May Be Produced and the Conditions for Which They Have Been Employed With Some Degree of Success

Withdrawal of hormones

- *Castration*
  - *Malignant neoplasms*
    - Mammary carcinoma
    - Prostatic carcinoma
    - Urinary bladder carcinoma
    - Testicular neoplasms
  - *Benign neoplasms*
    - Fibromyoma of uterus
    - Endometrioma
    - Desmoid tumor
    - Fibroadenoma
- *Adrenalectomy*
  - *Malignant neoplasms*
    - Mammary carcinoma
    - Prostatic carcinoma
- *Irradiation of the Hypophysis*
  - *Malignant neoplasms*
    - Mammary carcinoma
    - Prostatic carcinoma
- *Hypophysectomy*
  - *Malignant neoplasms*
    - Mammary carcinoma
    - Prostatic carcinoma

Administration of Hormones

- *Estrogens*
  - *Malignant neoplasms*
    - Mammary carcinoma
    - Prostatic carcinoma
    - Ovarian carcinoma
    - Cervix uteri carcinoma
    - Chorioepithelioma
- *Progesterone*
  - *Malignant neoplasms*
    - Cervix uteri carcinoma
    - Mammary carcinoma
    - Prostatic carcinoma
- *Androgens*
  - *Malignant neoplasms*
    - Mammary carcinoma
    - Cervix uteri carcinoma
    - Fundal carcinoma
    - Ovarian carcinoma
  - *Benign neoplasms*
    - Endometrioma
- *Adrenocorticotropin (ACTH) and Cortisone*
  - *Malignant neoplasms*
    - Mammary carcinoma
    - Prostatic carcinoma
    - Acute lymphatic leukemia
    - Chronic lymphatic leukemia
    - Plasma cell myeloma
    - Lymphosarcoma
    - Hodgkin s disease
  - *Benign neoplasms*
    - Keloid

gonadectomy has induced adrenal hypertrophy adrenal cortical tumors and frequently carcinoma of the mammary gland After gonadectomy, significant amounts of urinary estrogenic substances are still present in women and urinary androgenic substances in men The most important extragonadal source of these hormones is believed to be the adrenal cortex After adrenalectomy a further diminution in urinary excretion of androgenic and estrogenic substances may be observed These observations suggested investigation of the effect of adrenalectomy on sex hormone dependent neoplasms When substitution therapy became possible after the isolation of cortisone adrenalectomy became a practicable procedure The most promising results have been obtained in men and women with breast carcinoma Some patients with prostatic carcinoma have obtained palliation from adrenalectomy however by comparison with the results obtained in patients with carcinoma of the breast the number benefited and the extent of improvement is far less

HYPOPHYSECTOMY

The hypophyseal gonadotropic and adrenocorticotropic hormones through their effect on steroid hormone secretion are believed to influence the growth of certain neoplasms Prolactin a hormone elaborated by the adenohypophysis is believed to synergize with estrogen to stimulate mammary growth and lactation the *administration of prolactin can* induce lactation in some women with breast carcinoma regardless of the patient s age [74] Somatotropin the growth hormone also elaborated by the adenohypophysis may influence the growth of neoplasms By eliminating these hormones and their possible effects on certain neoplasms hypophysectomy can produce favorable effects The most promising results of this procedure have been obtained in men and women with advanced carcinoma of the breast

THE USE OF HORMONAL THERAPY FOR SPECIFIC MALIGNANT NEOPLASMS

Hormonal Therapy for Advanced Carcinoma of the Breast

CASTRATION

There is no evidence at present that prophylactic castration delays the appearance of metastases or increases the cure rate of patients who have undergone radical mastectomy for carcinoma apparently confined to the breast The use of this procedure has been advocated by some for patients with extensive axillary nodal involvement at the time of mastectomy however it is generally believed that castration should be reserved for use as a therapeutic measure until indications for prophylactic castration are more definitely established

Therapeutic castration has its greatest usefulness in menstruating women with widely disseminated metastases Surgical castration has the advantage of maximal suppression of gonadal hormone secretion in the shortest period Radiation castration can induce effective response in women near the menopause and should be used for patients whose condition does not warrant surgery For a more rapid castration effect testosterone propionate may be administered concurrently for two months since the desired effects of castration by x ray are usually obtained within this time The administration of androgen can induce amenorrhea but the hormone should not be used in preference to surgical or x ray castration Castration may be of value in the postmenopausal patient with a relatively high urinary excretion of estrogen or whose vaginal smear indicates estrogenic activity

Favorable response to castration may be obtained in about 30 per cent of patients with advanced carcinoma of the breast There may be relief of pain cough and dyspnea appetite may be increased and anemia and hypercalcemia may be corrected also calcification of osteolytic foci and regression of soft tissue lesions may be obtained [114] Regression of soft tissue cancer and x ray evidence of calcification of osteolytic foci may not be detectable for several months after castration All these changes do not necessarily take place in any one patient or at the same time The benefits are maintained for the most part for several months to a year some patients have maintained remission for several years (Figure 32 2 *A B*)

Ovariectomy occasionally is followed by acceleration of growth of the neoplasm in these instances it is possible that the ovaries exert a restraining influence on the growth of the carcinoma either directly or through hor

monal interrelationships with other endocrine glands possibly the adrenal or hypophysis Gonadectomy, by removal of this restraint could therefore permit the more rapid growth of the carcinoma

To predict the possibility of response to castration the following procedure has been suggested [76, 108] Over a period of several days small amounts of estrogen are administered to the patient, if exacerbation of the disease is induced (hypercalcemia hypercalcinuria malaise) the carcinoma is considered estrogen sensitive and favorable results may be expected from castration This test is applicable only when osseous metastases are present Some observers have not found this test effectual [74] further experience is necessary to evaluate this procedure

In men with advanced carcinoma of the breast orchiectomy may produce palliation [62 99] Since the testicular interstitial cells are apparently radioresistant roentgen castration rarely produces the desired effect on the neoplasm The testes can remain functionally active during the individual s lifetime therefore orchiectomy may be of value at any age The favorable responses are diminution of pain increase in strength and appetite and generally improved health and morale There may be regression of the primary tumor and of soft tissue metastases, calcification of osteolytic metastases may occur and there may be correction of hypercalcemia A larger percentage of men than women obtain favorable results from castration these effects however usually are of short duration as in women with carcinoma of the breast The improved condition is maintained for several years in an occasional patient (Figure 32 3)

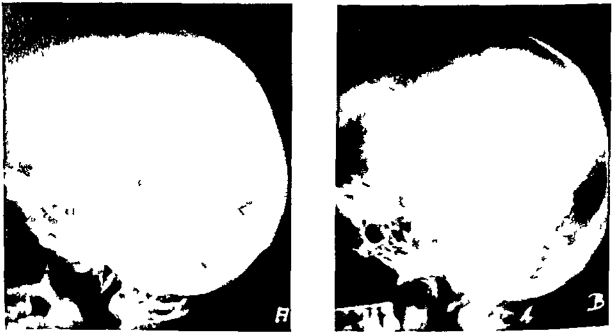


Fig 32 2 A Radiograph of the skull of a fifty-one year old woman with breast carcinoma showing osteolytic lesions This patient received roentgenotherapy to the lumbar spine and pelvis which produced permanent amenorrhea Pain in the lumbar region quickly subsided B Radiologic studies 2.5 years later revealed recalcification of all the osteolytic foci The effect on distant metastases such as that in the skull was undoubtedly a castration effect

ADRENALECTOMY [24 73 138]

Reactivation of breast carcinoma subsequent to castration induced regression has been attributed to stimulation by adrenal steroid hormones since the special steroids produced by the adrenal cortex resemble those of the gonads Ovariectomy has no immediate effect on urinary excretion of 17 ketosteroids indicating that they are of extraovarian origin probably from the adrenal gland [53] Also vaginal smear studies reveal a return of estrogenic activity subsequent to ovariectomy indicating estrogen production probably by the cortex of the adrenal

gland [11] Likewise subsequent to orchiec tomy there is usually a temporary fall in urinary 17 ketosteroids which after a time return to higher levels presumably as a con sequence of an increased production of ster oidal substances by the adrenal cortex [81 120] The resurgence of gonadomimetic sub stances is generally considered a factor in the reactivation of neoplasms that had been con trolled by gonadectomy Following adrenalec tomy there can again be a fall in the urinary 17 ketosteroids and in some instances re gressive changes in the neoplasm and improve ment of the patient

Men and women with advanced carcinoma of the breast who respond favorably to castra tion are considered those most likely to benefit from subsequent adrenalectomy however since favorable results have been obtained in patients who were not improved by castration or by other forms of hormonal therapy this cannot be considered a decisive criterion It has been suggested that the age group most likely to obtain benefit is between forty and sixty five years and that a long interval be tween mastectomy and appearance of metas tases increases the likelihood of remission Extensive cerebral hepatic or pulmonary cancer is considered a contraindication to the procedure however a few instances of symp

Fig 32-3 A sixty five year old man underwent a left radical mastectomy and was asymptomatic for three years Then pain was experienced in the right shoulder and lumbar region which finally incapacitated the patient Roentgenograms taken at this time revealed widely disseminated osteolytic lesions *(left)* Bilateral orchiectomy was performed Within two weeks there was diminution of pain and roentgenograms taken three months after castration revealed evidence of calcification in the osteolytic foci *(right)* The patient was rehabilitated and returned to work The improved status was maintained for a year then symptoms recurred the patient retrogressed rapidly and died of cancer

tomatic and objective regression of intracranial metastasis subsequent to bilateral adrenalectomy have been reported

A test has been devised to predict which patients may be helped by adrenalectomy [76] Cortisone is administered over a period of several days in order to depress adrenal cortical function If there is diminution in the amount of serum calcium or urinary calcium excretion or if the patient is symptomatically improved it is presumed that the patient may benefit from adrenalectomy This test requires further investigation

Special preoperative and postoperative hormonal management is required for patients who undergo adrenalectomy Cortisone acetate 100 mg is administered orally 48 and 24 hours before operation and 100 mg intramuscularly the day of operation during the surgical procedure it may be necessary to add cortisone to the intravenous infusion Postoperatively the patient receives 100 mg of cortisone acetate intramuscularly daily for 2 days 100 mg of cortisone is then administered orally decreasing the dose 25 mg daily until an oral maintenance dose of 37 5 to 50 mg daily is reached Fluorohydrocortisone 0 1 mg daily is employed to prevent salt loss

About 30 to 40 per cent of the patients are benefited by adrenalectomy The nature of improvement is similar to that after castration The remission is maintained for the most part for an average of 9 months an occasional patient has maintained the improved state for several years

Concurrent adrenalectomy and castration has been advocated by some At present however there is no evidence that the combined procedures produce a greater percentage of beneficial results or a longer duration of improvement than can be obtained from castration alone It would seem therefore that castration should be the therapeutic measure employed in the premenopausal women when reactivation of cancer occurs after mastectomy and that adrenalectomy should be considered when there is tumor reactivation after castration induced remission In postmenopausal patients beneficial effects have been obtained by adrenalectomy without ovariectomy

HYPOPHYSEAL IRRADIATION

There is some evidence that irradiation of the hypophyseal region may induce regression of breast carcinoma metastases [31 110] The writer studied a group of 10 patients with advanced breast carcinoma who received irradiation to the hypophyseal region 3 000 r in fractionated doses to each of 3 ports, a frontal and 2 temporal Permanent amenorrhea was induced in the menstruating women with some amelioration of pain and calcification of isolated osteolytic disease occurred in 2 of the premenopausal women All the patients ultimately died of the disease (Figure 32-4)

The use of the highly penetrating proton beam has caused destruction of the hypophysis with minimal injury to adjacent nerves and brain tissue and in some patients regression of breast carcinoma metastases was obtained This therapeutic procedure requires further study

Another modality used to destroy the hypophysis is radium emanation Gold seeds containing radon are introduced by way of the nose through the sphenoidal sinus into the sella turcica This procedure is believed to have low morbidity and mortality but its value is at present undetermined

HYPOPHYSECTOMY

Surgical removal of the hypophysis is one of the more recent procedures employed for the treatment of patients with advanced carcinoma of the breast Since the hypophysis described by some as the master endocrine gland is considered to regulate the production and release of steroid hormones it was believed logical that hypophysectomy could produce effects obtained from both castration and adrenalectomy and in addition eliminate the production of hormones such as prolactin and somatotropin which may possibly stimulate the growth of breast carcinoma The administration of somatotropin to a hypophysectomized woman with metastatic breast carcinoma is reported to have stimulated growth of the lesions [109]

Patients with reactivated disease after castration induced regression of the neoplasm have obtained further remission from hypophysectomy Women in the early menopausal

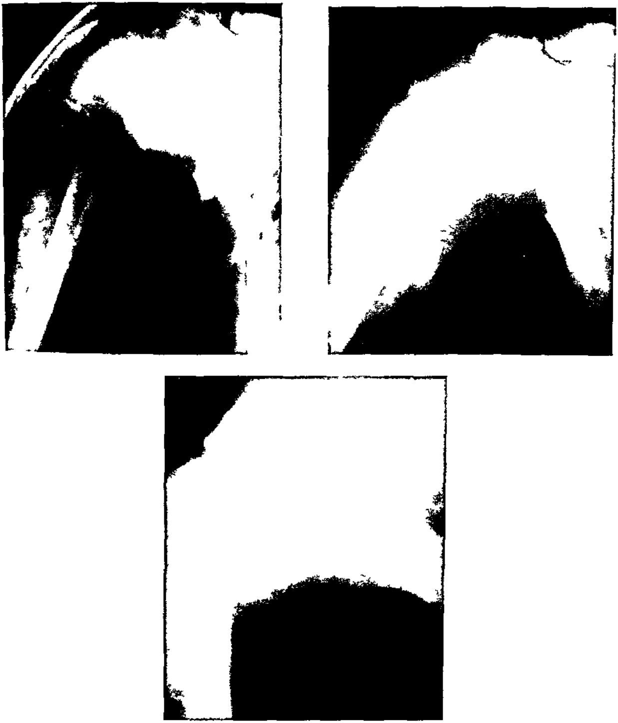


Fig 32-4 A fifty year old woman menstruating regularly had widespread osteolytic lesions and pathologic fractures secondary to carcinoma of the breast The roentgenogram (*upper left*) was made four months after the cast had been applied There is no evidence of calcification or callus formation The patient then received irradiation to the hypophysis 200 kv 3 000 r in air to each of two temporal and one frontal port Roentgenogram (*upper right*) was taken four months after completion of hypophyseal irradiation there is evidence of calcification of the head and neck of the humerus Roentgenogram (*lower*) taken nine months after completion of hypophyseal irradiation reveals dense calcification in some osteolytic foci other foci in the shaft have not recalcified The patient died of the cancer ten months subsequent to the hypophyseal irradiation

years and those not older than sixty years are believed to have a greater likelihood of favorable response Cerebral and hepatic metastases are considered contraindications for the procedure

The beneficial effects of hypophysectomy are of the same nature apparently, as those induced by castration and by adrenalectomy About 40 to 50 per cent of the patients obtain either subjective or objective improvement or both The most striking improvement has been the relief of pain [89, 109] The average duration of the improved state is about 8 months in one reported series, some patients are maintained in remission for several years

The preoperative and postoperative cortisone management of these patients is similar to that of the adrenalectomized patient In addition the hypophysectomized patient is maintained on thyroid 3 to 5 gr daily, and vasopressin (Pitressin) when necessary—the latter for control of diabetes insipidus which is reported to be severe in about 50 per cent of these patients

Some have suggested hypophysectomy as the primary therapeutic procedure for selected patients with advanced mammary carcinoma However much more experience is necessary to determine the optimal time in the course of the disease for its use and to evaluate its effects With the knowledge available at present it would seem that the primary therapeutic measures should be the simpler procedures and that when these are no longer effective or have failed procedures such as adrenalectomy and hypophysectomy should be considered

ESTROGEN THERAPY

The administration of steroid hormones depresses the production of gonadotropic and other hypophyseal hormones [16 34 43, 136] Among other results is a diminished gonadal steroid hormone secretion which may induce effects on breast carcinoma similar to that of gonadectomy or hypophysectomy [97]

The greatest usefulness of estrogen therapy is in women five or more years postmenopause either spontaneous or induced The hormone is of particular value in patients with soft tissue metastases Its use in menstruating or recent postmenopausal women and on occasion in women well past the menopause may accelerate the disease process [4 5 58] This may be the result of producing a hormonal environment favorable to the growth of the neoplasm or of a direct stimulating effect on the neoplastic cells The rapid growth of breast carcinoma in the pregnant patient may be due to the presence of placental estrogen It has been reported however that massive doses of estrogen 1 000 mg daily induced amenorrhea and favorable effects in some menstruating women This regimen warrants further investigation

Treatment Plan

A satisfactory treatment plan is the oral administration of 15 mg of diethylstilbestrol daily, in divided doses Some patients may not tolerate this drug but may have no difficulty with the natural hormone preparations such as ethinyl estradiol which can be administered orally, 1 mg three times a day or estrone sulphate, 10 mg orally three times a day The parenteral administration of estradiol dipropionate 5 mg twice a week, is an effective therapeutic regimen for some patients

A favorable response may be obtained within a few weeks however most patients require three to four months of treatment and for an occasional patient a longer treatment period may be required If no favorable response is obtained after three or four months continued estrogen therapy is usually ineffective Patients responsive to estrogen therapy should receive the hormone as long as remission is maintained When the diseas reactivates an occasional patient may obtain an additional period of remission by the us of androgen

Favorable Effects of Estrogen Therapy

About 40 to 50 per cent of the patients obtain objective regression of disease and most of these patients also obtain relief of symptoms Hematopoiesis mav be stimulated with correction of an existing anemia and in some instances polycythemia is induced [127] The anabolic properties of estrogen may correct weight loss About half of the patients with soft tissue lesions obtain healing of ulcerations and regression of soft tissue tumors such as skin nodules involved lymph nodes and the

primary carcinoma [22 58 98] Of the patients with pulmonary metastases about 30 per cent show regression of the lesions which is especially gratifying when compared to the response obtained with androgen in patients with pulmonary metastases (Figure 32 5)

Regression of soft tissue lesions may be the result of the desmoplastic action of the hormone the fibrosis enmeshes the cancer cells which frequently exhibit degenerative changes such as nuclear disintegration and vacuolization of the cytoplasm similar to that observed after intensive irradiation of breast carcinoma [38 41, 101]

obtained in about 20 per cent of the patients with osteolytic lesions some of which may be replaced by normal appearing trabeculations regression of soft tissue disease may be detected before the osteoblastic changes, the former changes may occur a few weeks to four months after treatment is instituted osteoblastic changes may require a long period and on occasion may not be evident for seven or more months which is longer than for a comparable change subsequent to androgen therapy *(quod vide)*

The improved state is maintained in most patients for several months to a year longer

Fig 32 5 A sixty five year-old woman had evidence of pulmonary metastases but no osseous involvement two years after a radical mastectomy for an infiltrating duct carcinoma Grade II She received 15 mg of diethylstilbestrol daily for five months for a total of 2 000 mg Comparison of roentgenogram at left made before instituting estrogenic therapy and that at right made after four months of treatment reveals regression of the pulmonary metastases

Estrogen causes retention of calcium a negative calcium balance in consequence of widespread osteolysis and loss of calcium through the urine and feces may frequently be corrected by the administration of estrogen [101 113] The retention of calcium favors redeposition of this mineral in the osteolytic foci of metastatic carcinoma with resultant diminution or disappearance of pain and lessened likelihood of pathologic fracture

Estrogen is thought to have a specific stimulating effect on osteoblasts It has been suggested that estrogen acts on bone metastases in a dual capacity by inhibiting the growth of the neoplasm and simultaneously or successively stimulating calcification and osteogenesis Calcification of osteolytic metastases is

periods of remission have been obtained in some patients One of the writer s patients a woman with osseous and soft tissue metastases was maintained in comfort for almost five years The favorable response to this therapy is more often obtained in the elderly women In a group of thirty six patients treated by the writer with 15 mg of diethylstilbestrol favorable subjective and objective response was obtained in fourteen patients (39 per cent) ten of these patients (71 per cent) were sixty years and older

In certain patients estrogen therapy may sensitize cutaneous metastases to subsequent x ray therapy and less irradiation is necessary with this therapeutic sequence There is suggestive evidence that patients who obtain

beneficial effects from estrogen therapy have a longer period of survival than those who fail to respond to this therapy

Other Effects of Estrogen Therapy

Undesirable effects induced by estrogen therapy may be retention of sodium potassium and chloride, with resultant edema these effects may be controlled by restriction of salt intake and the use of diuretics and cardiac drugs Urinary stress incontinence can be on occasion an extremely uncomfortable complication the discomfort may be ameliorated by the use of a vaginal pessary to support the bladder

Uterine bleeding due to estrogen stimulation or to withdrawal of the hormone may also be an undesirable consequence of estrogen therapy Bleeding due to stimulation often subsides spontaneously during treatment or if the daily dose of estrogen is increased If bleeding is not arrested by these methods estrogen therapy should be terminated For persistent bleeding curettage is indicated to eliminate the possibility of endometrial carcinoma

Fig 32-6 A fifty nine year-old woman seven years postmenopause developed generalized osteolytic metastases one year after radical mastectomy for carcinoma *(left)* Testosterone propionate 100 mg three times a week was administered for two months for a total of 2 400 mg The pain disappeared the patient became ambulatory and roentgenograms taken three months after institution of androgen therapy revealed calcification of the osteolytic lesions *(right)*

Hypercalcemia may be a serious consequence in the cachectic and nonambulatory patient and on occasion may terminate fatally this complication is discussed more fully under the section on androgen therapy

PROGESTERONE THERAPY

An occasional patient has obtained a favorable response to therapeutic administration of this hormone [130] The advocated

dose is 100 to 250 mg of progesterone in oil injected intramuscularly daily [45] The therapeutic value of this hormone has not as yet been established

ANDROGEN THERAPY

The value of androgen therapy as a prophylactic measure to prevent or delay recurrent or metastatic breast cancer has not been established Unlike estrogen therapy androgen may be administered to women of any age

The greatest usefulness of androgen therapy is in women at the menopause a few years postmenopause and in elderly women with predominantly osseous metastases Elderly women with predominantly soft tissue metastases preferably should be treated with estrogen The younger menstruating woman should be castrated preferably surgically if the cancer is inoperable recurrent or metastatic Androgen should be reserved for use in these women when disease reactivation occurs so as to obtain if possible an additional period of remission When bone metastases are localized roentgentherapy is the procedure of choice Androgen therapy should be reserved for patients with osseous metastases so extensive that it is not practicable to irradiate them

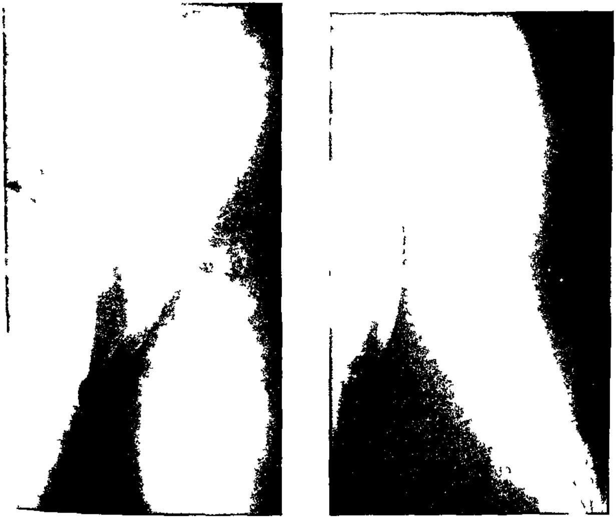


Fig 32-6 *(contd)* The patient remained asymptomatic for eight months and then pain recurred causing total incapacitation Radiologic studies at this time disclosed widespread bone dissolution *(left)* Estrogenic therapy was then instituted 15 mg diethylstilbestrol daily for a total of 1 600 mg over four months There was gradual diminution of pain and the patient became semiambulatory Roentgenograms taken eight months after institution of estrogen therapy revealed calcification of the osteolytic lesions *(right)* After this remission of eight months the cancer again became reactivated and the patient died 3 5 years after the first trial of hormonal therapy

An increased urinary excretion of estrogen sometimes follows the administration of androgen to postmenopausal or castrate women and suggests that in some instances androgen may be converted into estrogen and that it is the estrogen rather than androgen that produces the favorable results

Treatment Plan

A satisfactory treatment regimen is the intramuscular administration of testosterone propionate, 100 mg three times a week in some patients half of this dose has induced favorable effects [22] Favorable effects are usually obtained within six weeks in patients responsive to this treatment some patients obtain relief of pain within a few days to a week after treatment is instituted If no beneficial effects can be obtained after the administration of 3 5 Gm of testosterone propionate continued administration of the hormone rarely effects a favorable response

Two general plans of treatment may be used One plan is to administer androgen until favorable response is obtained usually within eight to twelve weeks the hormone is then withdrawn and therapy is discontinued during the period of remission a variation of this procedure is to continue administering the hormone until the regressive changes become stationary and then to withdraw the hormone Continued treatment often is unnecessary and uncomfortable for the patient The other plan of treatment is to continue administering the hormone after improvement is obtained using either the initial dosage schedule or small so called maintenance doses The writer prefers the plan of interrupted hormone administration

The favorable effects of this therapy are maintained in general for several months to a year some patients have maintained the improved state for several years Reactivation of cancer may be checked and an additional period of remission obtained in some patients by the resumption of androgen therapy by the administration of estrogen in the postmenopausal women and by withdrawal of the hormone in the continued hormone administration plan of therapy (Figure 32 6)

Other methods of androgen administration have been employed methyltestosterone orally 100 to 200 mg a day, or sublingually 50 to 100 mg a day, and implantation of 500 to 1,000 mg of crystalline testosterone in pellet form Methyltestosterone may induce regressive changes in the neoplasm and an improved state in some patients and crystalline testosterone may induce beneficial effects in an occasional patient allergic to the propionate or intolerant of large amounts of methyltestosterone Oral administration of androgen has the disadvantage of rapid drug excretion and on occasion, methyltestosterone may induce jaundice The propionate is in an oil medium absorption and excretion are prolonged and a more uniform and prolonged blood level of the hormone is obtained

Favorable Effects of Androgen Therapy

Symptomatic improvement is obtained in a larger percentage of patients after androgen than estrogen therapy and regressive changes in osteolytic disease are induced within a shorter period of time and in a higher percentage of patients Regression of soft tissue neoplasia especially pulmonary metastases is more effectively induced by estrogen

Symptomatic improvement may be obtained in over 60 per cent of the patients and objective improvement in about 30 per cent Calcification of osteolytic metastases some of which may regain normal bone trabeculation is evident to a greater or lesser degree in about 25 per cent of the patients with osseous metastases, objective evidence of pulmonary disease regression is observed in less than 5 per cent of patients with these metastases Stimulation of hematopoiesis with correction of an existing anemia can be obtained to a greater degree with androgen than with estrogen therapy Cerebral metastases seldom and hepatic metastases only occasionally regress with either hormone

Androgen induces protein production either by stimulation of anabolism or by inhibition of catabolism The resultant muscle formation counteracts to some extent the weakness and cachexia associated with advanced carcinoma and is a factor in producing a sense of well being in the patient The anabolic reaction may also be a factor in the deposition of fibrous tissue in areas of osteolysis This may interfere with the nutrition of

the cancer cells resulting in their devitalization and the fibrous matrix may also act as a framework for the deposition of calcium resulting in calcification of osteolytic foci

Roentgen evidence of calcification may not appear until three or four months after institution of treatment An early indication of bone regeneration may be a rise in the serum alkaline phosphatase value and can precede roentgen evidence of calcification [47] There may be progression of osteolytic disease in one area with disease regression in another area

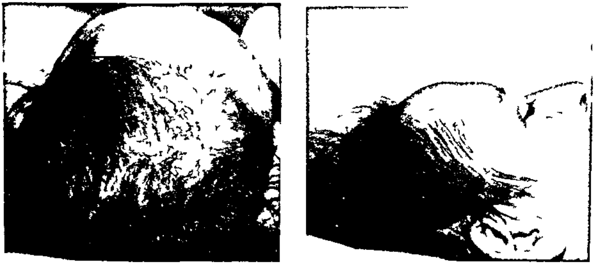


Fig 32 7 A thirty seven year-old woman with widespread osteolytic metastases from a breast cancer received 2 400 mg of testosterone propionate over a period of two months Amenorrhea was produced and the patient complained of falling hair that began three weeks after hormonal therapy was instituted The photograph at right was taken two months after termination of androgenic therapy and shows the alopecia and high forehead due to recession of the hair line

Many patients however despite the appearance of new metastatic foci maintain favorable subjective response

Cessation of menses during androgen therapy so-called chemical castration has certain physiologic and psychologic advantages in certain patients the hormone induced amenorrhea is temporary and the menopausal symptoms usually are less intense than those associated with surgical roentgen castration

Other Effects of Androgen Therapy

Acne hoarseness alopecia clitoral hypertrophy virilism salt retention and edema are some of the consequences of androgen therapy Hoarseness and virilism may persist the other effects are for the most part reversible Increased libido under certain circumstances can create a difficult problem (Figure 32 7)

Hypercalcemia occurs in about 10 per cent of semiambulatory or immobilized cachectic patients with osteolytic cancer This unfavorable effect may occur spontaneously or subsequent to estrogen or androgen therapy [36 60 126] on occasion the steroid hormones apparently accelerate neoplastic growth Hormonal stimulation of the cancer process appears to be accelerated by immobilization of the patient possibly the opposite obtains the mobilization of calcium is initiated by immobilization of the patient and accelerated by administration of the hormone The mobilized calcium is excreted through the kidneys which may be unable to eliminate the large quantities so that hypercalcemia results There may be pre-existent renal damage in some patients and in others the kidneys may be damaged by the heavy load placed upon them [60]

Hypercalcemia is characterized by lethargy and increasing depression associated with nausea vomiting and a progressive rise of the serum calcium and frequently of the blood urea nitrogen levels The condition must be corrected for it can terminate fatally and the patient can die in uremia In some patients repeated episodes of hypercalcemia can occur (Figure 32 8)

Treatment is directed toward reduction of

calcium intake, hydration of the patient correction of electrolyte imbalance, and conversion of the ionized serum calcium into a soluble nonionized form If hypercalcemia occurs during hormone therapy, the hormone should be withdrawn however, it has been reported that in an occasional patient spontaneous hypercalcemia may be corrected by administration of the hormone, this procedure usually aggravates the condition

Reduction of hypercalcemia has been obtained by specific medication Sodium citrate 2 5 per cent solution is administered intravenously, in amounts of 250 cc every four to six hours until improvement is obtained [60] however this treatment must be used with caution since in the presence of impaired kidney function large amounts of sodium citrate may produce alkalosis Cortisone acetate in daily doses of 100 to 250 mg administered intramuscularly has corrected hypercalcemia in some patients chelating agents have produced temporary reduction of hypercalcemia but serum calcium quickly returns to pretreatment levels [124]

In an effort to obtain androgenic substances with greater effectiveness and fewer undesirable consequences than the androgens in current use new compounds have been synthesized In general the effectiveness of the hormone depends upon its androgenic potency, the newer potent androgenic substances have not been superior to testosterone in their effect on neoplasia and have the same virilizing effects those with lesser androgenic activity have been in general less virilizing but also have been less effective [44]

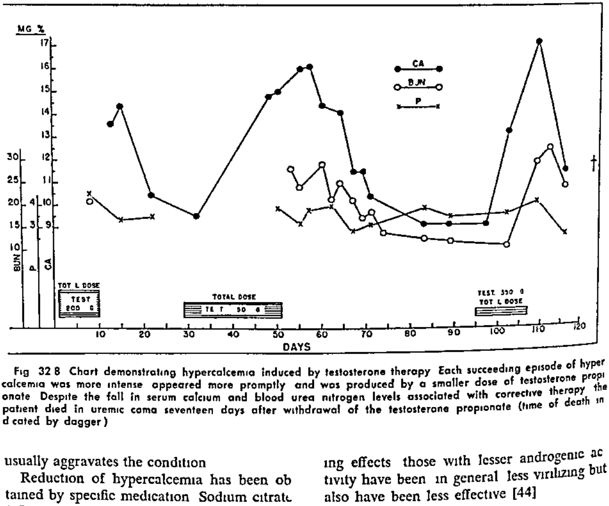


Fig 32 8 Chart demonstrating hypercalcemia induced by testosterone therapy Each succeeding episode of hypercalcemia was more intense appeared more promptly and was produced by a smaller dose of testosterone propionate Despite the fall in serum calcium and blood urea nitrogen levels associated with corrective therapy the patient died in uremic coma seventeen days after withdrawal of the testosterone propionate (time of death indicated by dagger)

CORTISONE THERAPY

The oral administration of cortisone acetate in daily doses of 200 mg has induced regression of mammary carcinoma metastases [129] some advocate doses as large as 400 mg daily [32] A favorable response similar to that produced by gonadal steroid hormone therapy has been observed in some patients and regression of pulmonary metastases has been obtained Remission for the most part is maintained for only a few months There is some evidence that newer corticosteroid sub

stances such as prednisone and prednisolone administered daily in doses of 100 mg have greater analgesic properties and a greater ability to ameliorate the effects of cerebral metastases than has cortisone

The effects on the carcinoma of large doses of corticoids may result in part from depression of adrenocorticotropic hormone (ACTH) secretion by the hypophysis with a resultant diminution of adrenal cortical steroid hormone production This so called medical adrenalectomy is much less effective than surgical removal of the adrenal glands

ESTROGEN THERAPY FOR ADVANCED CARCINOMA OF THE BREAST IN MEN

The administration of estrogen to men with breast carcinoma depresses the secretion of hypophyseal gonadotropic hormone with a resultant decrease in androgen production by the testes and in a manner comparable to orchiectomy deprives the androgen sensitive carcinoma of its growth influencing hormone Calcification of osteolytic foci and regression of soft tissue lesions have been induced in some men with advanced breast carcinoma by the administration of estrogen as the initial therapeutic procedure [62] A satisfactory treatment regimen is administration of diethyl stilbestrol orally 5 mg three times a day continued for as long as remission is maintained or for as long as the patient will tolerate the hormone Hypercalcemia electrolyte and fluid retention as well as painful gynecomastia can be consequences of estrogen therapy hypercalcemia and retention of electrolytes and fluid are treated in the same manner as when they occur in women after estrogen therapy

Surgical castration is a simple procedure in men and is the preferred initial therapeutic measure in men with advanced carcinoma of the breast When there is reactivation of cancer after a period of remission induced by orchiectomy the use of estrogen may produce an additional remission period

GENERAL COMMENTS ON HORMONAL THERAPY OF CARCINOMA OF THE BREAST

In the previous sections individual measures used in the treatment of advanced breast carcinoma were discussed The following are some general observations on hormonal therapy

Reactivation of disease during hormonal therapy of a carcinoma controlled initially by estrogen or androgen may be counteracted in some patients by withdrawal of hormonal therapy

A correlation between response to hormonal therapy and histologic grade of malignancy has been suggested the lower grades being considered more responsive to treatment [88] At present this supposition has not been substantiated but further study of the possible relationship is indicated

There appears to be some correlation between the state of nutrition of the patient and the response to hormonal therapy A comparative study by the writer of hospitalized and nonhospitalized breast carcinoma patients on the same regimen of either estrogen or androgen therapy demonstrated that a larger percentage of the nonhospitalized patients were improved by the treatment [63] The hospitalized patients for the most part had more advanced cancer were it a poorer state of nutrition and had a shorter life span after institution of therapy than did the nonhospitalized patients Since the late stages of the cancer are associated with severe inanition and with serious disturbances of protein and calcium metabolism the poor response to hormonal therapy of patients with advanced cancer may be due in part to these factors It may be that better results from hormonal therapy could be obtained by correcting as far as possible physiologic disturbances such as anemia vitamin deficiency hypoproteinemia and electrolyte imbalance

Many factors inherent in the cancer and in the host and the reactions of each upon the other influence the effects of hormonal therapy These effects are varied and subtle and probably introduce many changes of which we are at present unaware It is quite likely that no two carcinomas or their host react identically to apparently identical measures of hormonal alteration even though apparently similar results are observed

There is diversity of opinion concerning the advisability of prophylactic hormonal therapy [67 68 112 122] The beneficial effects of an altered hormonal state are relatively

transitory, possibly because there is subsequent establishment of a less labile state of hormonal equilibrium, adaptation of the organism to the hormone so that favorable physiologic changes are reversed, or evolution of tumor cells resistant to the changed hormonal environment. Some believe, therefore, that an altered hormonal substrate prematurely created may deprive the patient of a therapeutic aid if and when the need should arise. Contrariwise, it has been suggested that if the altered substrate creates an environment unfavorable for the growth of the cancer cells, this may delay the appearance of recurrences and metastases until cancer cells resistant to the environment gain ascendancy. The value of prophylactic hormonal therapy has not as yet been established, and further study of the effects of this procedure is necessary.

There are various procedures for the treatment of advanced breast carcinoma and general rules for their use. To obtain optimal results it is essential to use these measures judiciously and to individualize their application. The proper time to initiate therapy, the most advantageous procedure to use, and the optimal sequence of therapeutic measures must be determined for each patient.

The judicious use of roentgentherapy can obtain long periods of comfort for many patients. Radiation therapy should be used for localized cancer foci, and when this agent is no longer practicable because of wide dissemination of cancer, the use of hormonal measures should be considered.

At present there is no evidence that concurrent use of hormonal measures, as for example androgen and estrogen therapy or castration and androgen [122], produces an additive effect. A study by the writer of the results obtained by therapeutic castration and the concomitant administration of androgen did not demonstrate an increase in the percentage of patients benefited or prolongation of the improved state beyond that obtained by the individual use of each procedure [63]. Also, there is no evidence at present that the combined use of castration and adrenalectomy for women in menstrual life has produced improvement in a higher percentage of patients or a longer duration of improvement

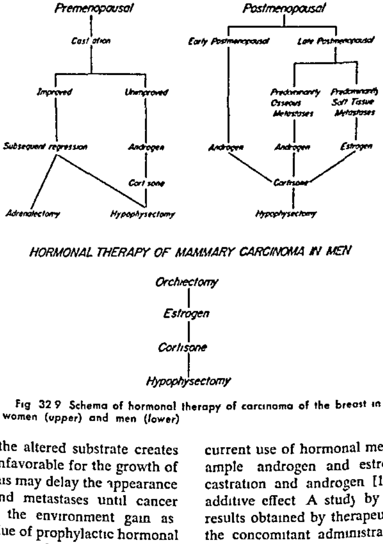


Fig. 32.9. Schema of hormonal therapy of carcinoma of the breast in women (upper) and men (lower).

than has been obtained by the use of castration alone

Until there is evidence to the contrary it would seem that the various procedures for altering hormonal relationships should be employed individually, utilizing another measure when one is ineffective or no longer effective By this plan of therapy it may be possible to obtain longer periods of palliation The percentage of patients benefited and the duration of favorable response obtained from the use of the different hormonal measures do not vary greatly (progesterone and cortisone excepted) It would therefore seem logical in the present state of our knowledge to use the simpler procedures initially and in the event of failure or regression of improvement to consider the use of more involved procedures

Figure 32 9 shows a general plan for hormonal therapy of advanced mammary carcinoma it should be altered to meet the requirements of the individual patient

Hormonal Therapy for Endometrial Carcinoma

The incidence of uterine carcinoma is second to carcinoma of the breast and its highest prevalence is in the postmenopausal years There is some evidence that estrogen stimulation may be a factor in the etiology of this disease but there is a diversity of opinion on this point In women with estrogen secreting ovarian tumors the frequency of endometrial carcinoma is higher than for the female population in general often there is a history of prolonged menstrual life in these patients with atypical bleeding and minimal menopausal symptoms suggestive of prolonged estrogen secretion The occurrence of endometrial carcinoma is unusual in castrate women

Since androgen can depress the growth and the secretory activity of endometrial epithelium it was thought that this hormone could induce regression of cancer arising from this tissue Regression of pulmonary metastasis after the administration of 3 300 mg of testosterone propionate has been reported [39] in general however the results of this therapy have been disappointing Progesterone therapy has induced in an occasional patient regression of soft tissue metastases however the effects of this therapeutic agent also have been disappointing

Hormonal Therapy for Uterine Chorioepithelioma

This neoplasm is often associated with an increased excretion of gonadotropins of chorionic origin to depress production of these substances large amounts of estrogen have been administered Diethylstilbestrol administered to two women with disseminated chorioepithelioma induced temporary subjective improvement and regression of pulmonary metastases in one patient and regression of vaginal metastases in the other both died of the disease within a year of its recognition [77 88] Testosterone therapy has not been successful

Hormonal Therapy for Cervix Uteri Carcinoma

Testosterone propionate has been administered to a few patients with advanced carcinoma of the cervix uteri [9] Relief of pain and a feeling of well being were obtained in some patients this may have been due to the general anabolic effect of the hormone rather than to a specific effect on the neoplasm No objective or histopathologic evidence of regression was observed

Some carcinomas of the cervix uteri initially resistant to roentgentherapy have been sensitized to irradiation by the administration of testosterone during the course of x ray therapy [7]

Regression of carcinoma of the uterine cervix has been induced by intensive progesterone therapy 250 mg of progesterone in 5 cc of oil intramuscularly administered daily for varying periods up to 170 days [65] There was considerable regression of the neoplasm and cessation of bleeding and vaginal discharge in both early and advanced stages of the disease In a number of patients radical surgical procedures were performed after hormonal therapy however the hormonal procedure did not produce cure of the disease since in specimens surgically removed and those examined postmortem there was evidence of carcinoma The possible future value of progesterone therapy for uterine cervix

carcinoma is indicated by the reported favorable response, however, until further experience validates this therapeutic measure, established initial procedures should be employed and the hormone reserved for reactivated disease

Hormonal Therapy for Ovarian Carcinoma

Regression of ovarian carcinoma metastases subsequent to androgen therapy has been reported [141] The writer administered testosterone propionate in doses of 2 500 to 3,500 mg to some patients with late cervical cancer and to others with advanced ovarian carcinoma and obtained a transient favorable subjective response, possibly owing to the anabolic effect of the hormone There was however no effect observed on the tumor growth or the course of the disease, similar results have been reported [9, 17]

In an occasional patient estrogen therapy has induced regression of ascites pulmonary hepatic and lymph nodal metastases

The granulosa cell tumor secretes estrogen and the arrhenoblastoma secretes androgen both are relatively uncommon neoplasms Treatment of advanced stages of these neoplasms with the counteracting steroid hormone may be of some palliative value however this type of therapy has not as yet been reported

Hormonal Therapy for Thyroid Carcinoma

In some primitive vertebrates the thyroid gland is part of the uterus [42] the two have become separate organs in the process of evolution but the relation still exists as indicated by increase in size and activity of the human thyroid gland during pregnancy and the tendency of the hypothyroid patient to be sterile or to abort It would seem therefore that gonadal hormone therapy for thyroid gland carcinoma is a logical procedure In one woman with metastatic adenocarcinoma of the thyroid gland there was suggestive evidence of calcification of osteolytic metastases and symptomatic improvement after treatment with testosterone propionate [85] Further study of androgen therapy for women with this neoplasm is indicated

Estrogenic hormone may possibly be of value in men with advanced thyroid cancer

BENIGN NEOPLASMS

Hormonal Therapy for Fibromyoma of the Uterus

In most instances uterine fibromyomas regress after the menopause or castration Fibromyomas that produce symptoms are best treated by surgical removal or by hysterectomy roentgen or radium castration should be the procedure for patients considered poor surgical risks however curettage should first be performed to establish the presence or absences of malignant neoplasm

Androgen can restrain the growth and secretory activity of endometrial epithelium and can inhibit the development of the spiral arteries which control menstrual bleeding [28] Excessive functional bleeding or bleeding from fibromyomas often can be diminished or arrested by the administration of testosterone and regression of fibromyomas may in some instances be obtained Favorable effects can be obtained by the intramuscular administration of testosterone propionate 25 mg three times a week or by the oral administration of methyltestosterone 10 mg three or four times a day when bleeding is diminished or arrested the dosage may be decreased and ultimately therapy can be terminated

Hormonal Therapy for Endometrioma

Endometrioma usually occurs in young nulliparous women and may produce intense dysmenorrhea and often menorrhagia the tumor associated with endometriosis is considered estrogen sensitive Histologically considered benign this neoplasm has some attributes of malignancy rapid growth invasiveness and the capacity to metastasize Endometrioma usually produces dense adhesions that may cause stricture of the sigmoid colon After castration surgical or radiologic [33] the tumor may regress however the fibrosis is uninfluenced by estrogen withdrawal and surgical intervention may be necessary to relieve obstruction

Favorable results have been obtained with androgen therapy and this measure may be

useful for women who hope ultimately to become pregnant but need symptomatic relief [66] Doses of 500 mg of testosterone propionate administered during the entire menstrual cycle or during the first two weeks of the cycle usually induce amenorrhea and amelioration of symptoms however masculinization may result Alleviation of symptoms without production of amenorrhea and masculinization often may be obtained by smaller doses of the hormone

A satisfactory treatment regimen is 25 mg of testosterone propionate administered intramuscularly three times a week or oral administration of methyltestosterone 10 mg daily during the first two weeks preceding the onset of menstruation Treatment should be intermittent regardless of the method employed and used only long enough to control symptoms treatment is reinstituted when symptoms recur

Hormonal Therapy for Desmoid Tumors

Desmoid tumors usually arise from the rectus sheath of the abdominal wall Usually benign this fibrous tumor may be invasive locally and may exert its deleterious effect by progressive increase in size and pressure on occasion the tumor may undergo sarcomatous change [106] Although apparently influenced by estrogen it is not a tumor of the female generative organs It occurs predominantly in women often after pregnancy but has been found on occasion in men Surgery is the therapeutic procedure of choice For patients with recurrent disease or those considered poor surgical risks castration can be of benefit There is no reported experience with orchiectomy to the writer s knowledge, but the procedure would appear to be logical for the recurrent tumor in men

Hormonal Therapy for Fibroadenoma of the Breast

Surgery is the procedure of choice in the treatment of this tumor however excision is not feasible in patients with extensive painful adenomatous disease throughout both breasts For these patients termination of the menses by ovarian irradiation is indicated cessation of ovarian function usually induces regression of the adenomatous masses and relief of pain

Hormonal Therapy for Nonneoplastic Breast Disease

Fibrocystic disease of the breast (chronic cystic mastitis) is the most common abnormality of the breast found in women and is believed to be due to an estrogen progesterone imbalance that results in a relative or absolute excess of estrogen Clinically, a tender diffusely or discretely thickened breast is observed The common stigmas of carcinoma—skin dimpling nipple retraction and axillary adenopathy—can be observed in some patients Biopsy examination is essential for these patients

Pain is usually the chief indication for therapy Spontaneous regression of the lesions frequently occurs after pregnancy especially if the infant is nursed also after the menopause Reassurance that the condition is not malignant may reduce awareness of pain in some patients For symptoms that persist the following hormonal procedures may be employed progesterone administered orally 50 to 100 mg daily for the last 5 days of the menstrual cycle gonadotropic hormone by injection 500 to 1 000 I U daily from the 15th to the 24th day of the menstrual cycle or the oral administration of methyltestosterone 10 to 30 mg daily for 10 days Relief of pain frequently is obtained however the fibrocystic changes may not regress

THE USE OF HORMONES AS SUBSTITUTION THERAPY IN WOMEN WITH NEOPLASMS OF THE SEX ORGANS

Although the mechanism is yet to be determined it is believed by some that the hot flushes dizzy spells and emotional disturbances associated with the menopause are induced by diminished ovarian control of hypophyseal gonadotropic secretions [115] These manifestations often can be controlled by estrogen therapy The use of estrogen for symptoms of spontaneous or induced menopause in patients who have had breast carcinoma or cancer of the female generative organs is generally contraindicated in these patients estrogen may reactivate latent cancer since this hormone has been considered a factor in the growth of carcinoma of the breast and of the endometrium [21 40 135]

Distressing menopausal symptoms in these patients often can be controlled with phenobarbital 0 25 to 0 5 gr 3 times a day, or small amounts of methyltestosterone 10 to 30 mg a day administered sublingually, the androgen is used intermittently for short periods of time to prevent possible virilization [117] The patient is instructed to discontinue therapy during asymptomatic periods The combined use of the hormone and barbiturate frequently is more effective than the use of either drug alone Methyltestosterone 10 to 30 mg administered daily, often can control menopausal menorrhagia In some patients curettage may be indicated to eliminate the possibility of endometrial carcinoma

HORMONAL THERAPY FOR ADVANCED PROSTATIC CARCINOMA

Only 10 per cent of prostatic carcinoma is detected early enough to be treated by prostatectomy Pallative therapy therefore is of great importance in the management of this disease Indications for castration and for estrogen therapy are similar in the patient with cancer of the prostate in contradistinction to the various indications for their use in the patient with breast carcinoma Orchiectomy and estrogen therapy therefore will be considered together

Orchiectomy and Estrogen Therapy

The prophylactic use of hormonal therapy at time of or immediately after prostatectomy has been advocated by some immediate orchiectomy immediate institution of estrogen or a combination of both procedures is employed

Therapeutic hormonal measures for inoperable and metastatic carcinoma have been established however opinions vary with regard to timing and sequence of the procedures Some suggest immediate orchiectomy or estrogen administration or a combination of both as soon as the diagnosis is established whether or not the patient is asymptomatic others advocate withholding all therapy until symptoms occur from either the primary neoplasm or metastatic cancer The reason for the latter therapeutic plan are many patients have prolonged periods of freedom from symptoms despite extensive cancer the benefits of hormonal alteration are transient and premature change in hormonal equilibrium may deprive the patient of the benefits of this measure when symptoms appear

Of those who advocate treatment only when symptoms appear some prefer orchiectomy as the initial procedure, others prefer the initial use of estrogen The advocates of initial estrogen therapy believe this is a more physiologic measure than orchiectomy since the presence of the testes by controlling adrenocorticotropic hormonal production prevents an excess of androgen secretion by the adrenal cortex they believe the initial use of castration is indicated only when the severity of the symptoms necessitates immediate palliation

A satisfactory regimen of estrogen therapy *is the oral administration of diethylstilbestrol* 5 to 15 mg daily in divided doses the hormone is administered for as long as improvement is maintained or the drug can be tolerated The administration of estrogen for reactivated cancer after remission induced by orchiectomy seldom is effective, however for reactivated disease after remission induced by estrogen orchiectomy may be effective

The advocates of orchiectomy as the initial procedure believe that estrogen incompletely inhibits androgen production that estrogen must be administered for prolonged periods and that estrogen may be poorly tolerated Castration always should be surgical

FAVORABLE EFFECTS OF ORCHIECTOMY AND ESTROGEN THERAPY

The favorable responses after castration or after estrogen therapy are similar however the relief of symptoms is more rapid after castration Some patients experience relief of pain within 24 hours after the operation usually relief of pain after estrogen therapy is obtained one or two weeks after treatment is instituted The favorable effects which often are striking are obtained in about 75 per cent of the patients A gain in weight and sense of well being are the more immediate effects In about 50 per cent of the patients cessation of hematuria regression of soft tissue metastases and diminution in size of the primary carcinoma are obtained the primary neoplasm frequently regresses sufficiently to alleviate obstruction to urinary flow from the

bladder Roentgenologic evidence of osteolytic disease regression may subsequently be observed and normal bone trabeculation may appear

After orchiectomy there may be a decreased excretion of urinary 17 ketosteroids in some patients however the decrease may be slight or there may be none at all [120] Since some patients with little or no decrease in urinary 17 ketosteroids subsequent to orchiectomy obtain favorable effects from castration it has been suggested that some testicular biologically active nonandrogenic substances that are not excreted as 17 ketosteroids may be important factors in influencing carcinoma of the prostate [103]

The serum acid phosphatase which usually becomes elevated after the cancer breaks through the prostatic capsule may return to normal limits within twenty four to forty eight hours after orchiectomy Serum acid phosphatase activity is not depressed by castration in about 20 per cent of patients and these patients do not respond favorably to the procedure After estrogen therapy there may be a gradual drop in serum acid phosphatase levels Subsequent to either procedure there may be a rise in the serum alkaline phosphatase levels indicating osteogenic activity and normal appearing bone trabeculations may be found in foci of osteoblastic metastases [49]

In some instances an inoperable carcinoma may become operable [18 48] this is considered by some to be the most important effect of hormonal alteration therapy The optimal time for surgery is when maximal regression of the primary carcinoma apparently has been reached No patient should be operated on if the primary cancer has not diminished sufficiently to make the procedure feasible if there is evidence of distant metastasis or if the general condition of the patient is unsatisfactory

Life expectancy appears to be increased by these hormonal measures and it has been suggested that an occasional patient has been cured Study of a large group of patients with metastatic cancer demonstrated that 35 3 per cent survived three years after orchiectomy and 21 6 per cent survived five years [104] From this study it also was concluded that the most effective five year control of the cancer in patients free from metastases could be obtained by the combined use of orchiectomy and diethylstilbestrol that the combined procedure was not more effective than orchiectomy alone after the appearance of metastatic cancer Another study of a large group of patients did not substantiate these conclusions [116]

In general the duration of improvement in patients responsive to either orchiectomy or estrogen administration varies from several months to several years in most patients there is reactivation of cancer within three years

OTHER EFFECTS OF ORCHIECTOMY AND ESTROGEN THERAPY

There may be distressing and uncomfortable effects after orchiectomy—flushes palpitation nervous instability, however relief of pain when it occurs is so gratifying that almost all patients willingly endure these discomforts In an occasional patient gynecomastia a frequent effect of estrogen therapy may necessitate termination of treatment because of pain Electrolyte retention with resultant edema may occur on occasion after estrogen therapy and in rare instances liver damage associated with jaundice Hypercalcemia has not been reported probably because osseous metastases of prostatic carcinoma in contradistinction to those of breast carcinoma are predominantly osteoblastic

Carcinoma of the breast has been reported in some patients after estrogen therapy however the histologic appearance of these tumors and the presence of acid phosphatase in the cells would seem to indicate that they are prostatic carcinoma metastases [13] In an occasional patient the histopathology of the breast carcinoma has been reported to be primary [46]

Androgen Therapy

The use of androgen has been advocated for the treatment of advanced carcinoma of the prostate The reason for its use is that the ultimate depression by androgen of hypophyseal gonadotropic hormone secretion could effect a decrease in endogenous androgen production even though initially the hor

mone may stimulate the disease Improvement in a few patients treated with this hormone has been reported, however, the usefulness and safety of this therapeutic measure have not as yet, been evaluated

Progesterone Therapy

It is believed that the interstitial cell stimulating hormone (ICSH) influences androgen secretion by the testis and the adrenal cortex that progesterone suppresses hypophyseal secretion of ICSH, and that the administration of progesterone could induce depression of testicular and adrenal cortical secretion of androgen and produce the desired effect on prostatic carcinoma

Despite objections to this theory of progesterone activity the hormone has induced regression of disease and symptomatic improvement in some patients with untreated prostatic carcinoma and some with reactivated disease subsequent to castration or estrogen induced remission [48 133]

Cortisone Therapy

Amelioration of symptoms and regression of disease have been induced in some patients by the administration of cortisone The benefits obtained are similar to those observed in patients improved by adrenalectomy These favorable responses are believed to be due to depression of adrenocorticotropic hormone production by the hypophysis

Dosage of Hormones

Dosage of androgen progesterone and cortisone is similar to that employed in the treatment of carcinoma of the breast in women (*quod vide*)

Bilateral Adrenalectomy [54, 71, 73 138]

Since the gonads and adrenals are considered the principal sources of androgenic substances reactivation of prostatic carcinoma subsequent to remission induced by gonadectomy is believed to be the effect of adrenal cortical activity An increase in 17 ketosteroid urinary excretion that had decreased subsequent to gonadectomy is considered evidence of adrenal cortical activity and enlarged adrenal glands have been found in some patients subsequent to orchiectomy Bilateral adrenalectomy therefore was tried as a therapeutic measure for reactivated prostatic carcinoma An additional period of remission was obtained after adrenalectomy in some patients with disease that reactivated after a period of orchiectomy induced remission

Symptomatic improvement especially relief of pain has been obtained also regression of soft tissue and osseous metastases Decrease in serum acid phosphatase levels and in 17 ketosteroid urinary excretion was observed in patients responsive to adrenalectomy The percentage of patients benefited and the degree of improvement obtained do not approach those obtained by adrenalectomy in patients with carcinoma of the breast The preoperative and postoperative management of these patients is similar to that of patients adrenalectomized for breast carcinoma

Irradiation of the Hypophysis

Symptomatic improvement has been obtained by irradiating the hypophysis of some patients whose symptoms recurred after an initial remission obtained by orchiectomy [55 96] It is possible that this measure reduced or suppressed adrenocorticotropic secretion The beneficial effects however were of short duration

Hypophysectomy

Subjective and objective favorable responses have been obtained by hypophysectomy in an occasional patient Indications for the procedure are similar to those for hypophysectomy for advanced breast carcinoma The percentage of patients improved however is far less than that obtained in advanced breast carcinoma patients

HORMONAL THERAPY FOR ADVANCED URINARY BLADDER CARCINOMA

The frequency of this disease after the age of fifty is greater in men than in women Since the bladder and the prostate are of similar embryonic origin the benefits effected by estrogen therapy in prostatic carcinoma patients suggested the use of estrogen in patients with bladder carcinoma A few men with advanced cancer treated with estrogen obtained transient relief of pain reduction of urinary frequency, and of hematuria In some patients

there was cystoscopic evidence of tumor regression [50 51 86] An apparently primary carcinoma of the breast has been reported in one man subsequent to this therapy [93] The dosage of estrogen is similar to that employed for carcinoma of the prostate

Orchiectomy has resulted in relief of pain increase in appetite and strength decrease in hematuria and in urinary frequency and regression of bladder carcinoma in a few patients [121]

No patients have been cured by these procedures however one patient lived in relative comfort for three years despite recurrence of the tumor that previously had regressed subsequent to castration

HORMONAL THERAPY FOR TESTICULAR NEOPLASMS

Metastatic cancer that occurs after removal of a testicular neoplasm may be controlled temporarily in an occasional patient by removal of the remaining testicle In two reported cases one of which was a seminoblastoma pulmonary metastases regressed after removal of the second testicle however the duration of improvement after orchiectomy was only a few months in both cases [92]

GYNECOMASTIA

These enlarged breasts in men are often similar in configuration to a woman s breast An enlargement of the breast with milky secretion—so called witch s milk—is occasionally observed in the newborn of either sex and is believed to be produced by prolactin from the maternal circulation The condition subsides spontaneously within a week after birth and requires no treatment

With the exception of the condition described gyynecomastia occurs most frequently at puberty It can however be found in men of any age The breast enlargement varies from a small subareolar nodule to that of female configuration The gynecomastia of puberty usually disappears spontaneously after the age of 16 or 17 years however when the condition appears in later life it usually does not regress There may be bilateral breast enlargement but most frequently the enlargement is unilateral or more prominent in one breast

The gynecomastia of adolescence is believed to be the result of the androgen estrogen imbalance of pubescence In the adult the hormonal disturbance resulting in gynecomastia may be due to nutritional disturbances or to changes elsewhere in the body such as cirrhosis of the liver testicular or hypophyseal neoplasms feminizing adrenal tumors or treatment with or exposure to certain hormones such as estrogenic or androgenic substances gonadotropins and adrenal cortical hormones The etiologic factor for the most part cannot be determined

Many patients are asymptomatic others complain of tenderness of the breast Often the chief concern of the patient is embarrassment due to the appearance of the large breast or breasts It is important that the condition be differentiated from carcinoma in the older men This is relatively simple since in gynecomastia the mass is generally soft and the stigmas of carcinoma such as nipple retraction and skin attachment usually are absent

The treatment of choice is elimination of the cause whenever ascertainable Improved nutrition high protein diet administration of powdered liver and Vitamin B complex are thought to aid in the inactivation of estrogen by the liver and may be of value in some cases Hormonal therapy has not been found of value and the administration of testosterone may aggravate the existing condition by inducing proliferation of the mammary duct system Excision of the hyperplastic breast tissue is indicated for cosmetic and psychologic effects in some patients

THE USE OF HORMONES AS SUBSTITUTION THERAPY IN MEN WITH NEOPLASMS OF THE SEX ORGANS

THE MALE CLIMACTERIC

Orchiectomy like ovariectomy in women may induce symptoms of emotional and vasomotor instability flushes palpitation weakness irritibility and depression These symptoms can be controlled by the parenteral administration of small amounts of testosterone propionate [137] However since orchiectomy

is performed for carcinoma of the prostate and of the breast on the theory that these neoplasms are androgen sensitive and androgen stimulated this hormone should not be used in these patients The judicious use of barbiturates or estrogen alone or in combination often can ameliorate the symptoms of these patients

ADRENOCORTICOTROPIC AND ADRENAL CORTICAL HORMONE THERAPY

Malignant Disease of the Lymphatic System

Adrenocorticotropic hormone (ACTH) and adrenal cortical steroid therapy have benefited some patients with malignant disease of the lymphatic system The use of these substances for patients with other lymphomatous diseases—Hodgkin s disease lymphosarcoma or mycosis fungoides—has benefited relatively few of these patients There are no pretreatment criteria at present for determining which individuals will respond The most favorable response has been obtained in children with acute lymphatic leukemia in about 50 to 60 per cent of these children regression of disease and a sense of well being have been obtained

FAVORABLE EFFECTS

A few days after institution of ACTH or cortisone therapy for children with acute leukemia there may be a rapid fall in the number of leukocytes in the peripheral circulation a rise in the number of erythrocytes platelets and reticulocytes with cessation of bleeding from the mucous membranes a return of the sternal marrow cytology to normal appearance [35] and a concomitant sense of well being The period of remission is short however varying from several weeks to several months

Patients with acute leukemia whose disease becomes refractory to cortisone or ACTH may respond favorably to the folic acid antagonists—and vice versa This suggests that cortisone and the antifolic acid substances have different primary methods of action on the leukemic process [90] ACTH or cortisone therapy benefits an occasional adult patient with acute or chronic lymphatic leukemia There is some evidence that ACTH therapy may accelerate the disease process in other acute leukemias such as the granulocytic and monocytic types

Objective evidence of improvement may be decrease in size of lymph nodes liver and spleen, subjective evidence of improvement may be increase in appetite and sense of well being In Hodgkin s disease there may be remission of pyrexia and subsidence of pruritus The acquired hemolytic anemia which at times accompanies the leukemias and lymphomas may be corrected in some patients by ACTH or cortisone therapy [23]

Multiple Myeloma

Patients with multiple myeloma who benefit from ACTH or cortisone therapy experience diminution of pain and increase in appetite improvement may be observed *within* seven to fourteen days after treatment is instituted There may be a decrease in the amount of plasma protein and globulin and a reduction in the number of the bone marrow plasma cells a decrease in the percentage of marrow plasmablasts and an increase in the erythrocytes and hemoglobin in the circulating blood a decrease in the sedimentation rate and a diminution in excretion of Bence Jones proteins Hypercalcemia may be corrected and there may be a rise in serum alkaline phosphatase activity Roentgen evidence of osteoblastic change in the areas of osteolysis may subsequently be observed Remission may be maintained for many months [131] Favorable response apparently is obtained more often in patients with disease characterized by proplasmablasts and plasmablasts than in patients with mature myeloma cells When a favorable response can no longer be obtained by cortisone urethane may give an additional period of remission

Miscellaneous Connective Tissue *Neoplasms*

These hormones depress fibroblastic proliferation therefore their effects on neoplasms of connective tissue origin were studied There were no effects observed on fibrosarcoma and neurofibrosarcoma The hormones were also ineffectual on various other neoplasms such

as rhabdomyosarcoma synovioma and neuroblastoma [35]

Adrenocorticotropic hormone because of its antifibromatogenic properties has been used after excision of keloids to prevent their recurrence and in some instances of recurrent desmoid tumors There is some evidence that keloid production is diminished or prevented [20] however no effect has been observed on desmoid tumors [2] Injudicious use of the hormone may impede the process of healing

Dosage and Duration of Treatment With Adrenocorticotropic and Adrenal Cortical Steroid Hormones

In adults ACTH is administered intramuscularly daily 100 to 200 mg in divided amounts in children approximately one half of the dosage is administered Cortisone in adults is administered orally or intramuscularly as the acetate 100 to 200 mg daily in divided doses in children approximately one half of the dosage is used One therapy appears as effective as the other however cortisone has the advantage of oral administration Newer corticoids such as prednisone and prednisolone 100 mg daily administered orally or intramuscularly have produced favorable results in adults and appear to have less undesirable effects than cortisone Prednisone in doses of 1 000 mg daily is reported to have produced favorable response in adults with acute leukemia There was rapid disappearance of adenopathy and pleural effusion

Treatment with ACTH or the corticoids should be continued with diminished amounts of the hormones until the disease reactivates on occasion an additional period of remission may be obtained by increasing the dosage

Unfavorable Effects of ACTH and Corticoids

The possible deleterious effects of these hormones must be watched for and corrected whenever possible, if these cannot be counteracted therapy must be terminated Sodium retention and edema such as observed after sex hormone therapy frequently is found after ACTH and cortisone medication There may be hypopotassemia characterized by weakness and lethargy hypochloremia may occur and diabetes may result from diminished glucose tolerance There may be hypertension increased susceptibility to pyogenic infections wasting of muscles mental disturbance interference with wound healing and virilism may occur Peptic ulcers may bleed or perforate as a result of this treatment Patients with severe hypertension or with considerable emotional instability should not receive this type of therapy There is some evidence that these undesirable effects are less in degree with the newer corticoids prednisone and prednisolone

From this survey of hormonal therapy it is apparent that much can be offered the patient with advanced neoplastic disease—in palliation if not in cure palliation not only in terms of transient relief of pain but in temporary control of disease and a possible increase in survival period

The skill and judgment necessary for good diagnosis good surgery and good irradiation in the treatment of neoplasia in its less advanced stages is just as necessary for the choice and application of hormonal procedures for neoplasia in its more advanced stages Although there are general rules for hormonal therapy the best results can be obtained only by adapting these measures to the needs and responses of the individual patient The primary aim is to benefit the patient and for each patient with advanced cancer it is necessary to decide whether the extent of the benefits that can be expected are commensurate with the extent of the contemplated therapeutic procedure

CHAPTER 33

Principles of Clinical Cancer Chemotherapy

Alfred Gellhorn

In the early recording of medical history, the problem of cancer did not receive great emphasis The relative brevity of the life span the difficulties of diagnosing internal diseases, and the paucity of postmortem examinations are certainly among the factors that account for the apparent difference in frequency of neoplastic disease in the early centuries of civilized man s existence and contemporary man In the Egyptian Papyri however reference was made to ulcerating tumors of the skin and their treatment by local application of medicinal concoctions was recommended This early type of cancer chemotherapy has its counterpart today and now as then is an unsatisfactory method of treatment The objective of tumor chemotherapy is not the cure of localized disease but rather the destruction of disseminated neoplastic cells by a systemically administered drug

As cancer and its recognition became more frequent and the clinical problem of wide spread disease more pressing many ill fated attempts at drug therapy were made The development of curative surgical procedures and the introduction of x ray as a cancericidal weapon led to the well deserved abandonment of medicinal treatment of cancer at the beginning of this century Experience obtained in the past fifty years however has clearly demonstrated that the therapeutic problem of disseminated cancer continues to be a major medical challenge in spite of the impressive strides made by surgery and radiotherapy

The contemporary look of cancer chemotherapy bears little resemblance to its historic ancestors Throughout the world laboratory investigations assiduously search for potentially valuable antitumor drugs Compounds that have been found to inhibit neoplasms in experimental animals are characterized toxicologically and pharmacologically before submission for clinical trial Critical evaluation of candidate compounds against human tumors is carried out in small pilot studies and if preliminary results are encouraging independent investigation in other clinics precedes the distribution of the compound for general medical usage In spite of the fact that a specific drug has not yet been discovered that cures any type of human cancer chemotherapeutic agents are of value in the management of certain malignant neoplasms In the present chapter brief descriptions will be given of the various drugs in current clinical use and this will be followed by comments on their clinical application including their indications and limitations In other chapters many of these drugs will be discussed in greater detail both in terms of their pharmacology as well as their clinical application

DRUGS USED IN CLINICAL CANCER CHEMOTHERAPY

Alkylating Agents

The alkylating agents derive their name from the fact that their biologic activity depends upon a chemical reaction that is known as alkylation [9] The first alkylating drug to receive extensive clinical trial in cancer chemotherapy was nitrogen mustard and many of the compounds in this group are chemically related to it The alkylating reaction of nitrogen mustard with an amino acid is shown in Figure 33 1 In this series of reactions it can be seen that the first step is the transformation of nitrogen mustard to a cyclic

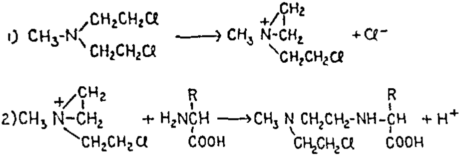
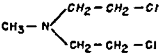
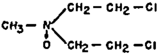
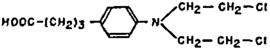
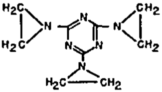
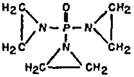
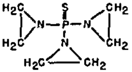


Fig 33 1 N trogen mustard (methyl b s β chloroethyl am ne HN) and its important chem cal transformat on and react on (1) The transformation of n trogen mustard to the chem cally reacti e ethylen mon um cat on (2) The alkylat ng reaction of the ethyl en monium cation with an amino acid

NAMES	*CHEMICAL NAMES*	*STRUCTURAL FORMULAS*
NITROGEN MUSTARD HN_2	METHYL BIS-(B-CHLOROETHYL) AMINE	
NITROMIN	METHYL-BIS-(B-CHLOROETHYL) AMINE-N-OXIDE	
CHLORAMBUCIL CB1348	N N-DI-2-CHLOROETHYL-γ-(p-AMINOPHENYL) BUTYRIC ACID	
TRIETHYLENE MELAMINE TEM	2 4 6-TRIETHYLENE-IMINO-s-*TRIAZINE*	
TEPA	N,N N -TRIETHYLENE PHOSPHORAMIDE	
THIOTEPA	N N N -TRIETHYLENE THIOPHOSPHORAMIDE	
MYLERAN	1 4-DIMETHANESULFONYLOXYBUTANE	$CH_3-SO_2O-(CH_2)_4-OSO_2-CH_3$

F g 33 2 Alkylating agents that are used in clin cal cancer chemotherapy

ethylenimonium cation This is the chemically reactive form of the drug and it has been demonstrated that nitrogen mustard reacts briskly with a variety of chemical groupings with biologic significance In the second step depicted in Figure 33 1 the ethylenimonium cation reacts with the amino group of the amino acid After this has occurred the second side chain of the nitrogen mustard can undergo cyclization as did the first and another molecule of amino acid be alkylated

Figure 33 2 presents those alkylating agents that are currently being used widely in clinical cancer chemotherapy As can be seen all of them are related to nitrogen mustard either through modification of the radical attached to the nitrogen or through congeners related to the ethylenimonium derivative The exception is Myleran a dimesyl compound which is also active as an alkylating agent

It has been determined that the mechanism of action of the alkylating agents is a direct chemical reaction with formed nucleic acids thereby altering the function of these essential cellular components [28] Although these compounds have a greater cytotoxic effect on certain neoplastic cells than on normal cells they all share the major toxic reaction of depression of bone marrow function Owing to differences in route of absorption and to quantitative variation in toxicity the several alkylating agents have greater usefulness in some neoplastic diseases than in others These will be mentioned in the section on clinical application

The Antimetabolites

Extensive studies on the mechanism of action of nitrogen mustard focused attention on the nucleic acids as important targets for antitumor drugs This concept received significant impetus following the introduction of the folic acid antagonists when it was shown that these compounds interfered with the biosynthesis of the nucleic acids [26] The folic acid analogs or antagonists are closely related chemically to folic acid as can be seen in Figure 33 3 which depicts folic acid and the analog most commonly used in clinical cancer chemotherapy methotrexate or Amethopterin

Another group of compounds that effectively interfere with the synthesis of nucleic acid by the cell are related chemically to one of the normal components of nucleic acid, namely the purines [12] Although many purine analogs have been synthesized the one compound that has demonstrated its usefulness in the treatment of human neoplastic

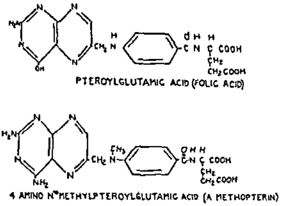


Fig 33 3 The structural formula for folic acid and the analog methotrexate which is used in cancer chemotherapy

disease is 6 mercaptopurine or Purinethol This compound is shown in Figure 33-4 and its relationship to adenine a normal constituent of nucleic acid is apparent The antitumor compound differs only in the substitution of an SH group for the amino group in the 6 position

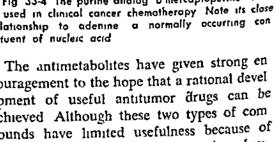


Fig 33-4 The purine analog 6 mercaptopurine which is used in clinical cancer chemotherapy Note its close relationship to adenine a normally occurring constituent of nucleic acid

The antimetabolites have given strong encouragement to the hope that a rational development of useful antitumor drugs can be achieved Although these two types of compounds have limited usefulness because of their toxicity to hematopoiesis they have made very important contributions to normal cellular biochemistry through their use as tools for the clarification of fundamental cellular enzymatic reactions

Hormones

The great tumor biologists Leo Loeb and A Lacassagne demonstrated the importance of hormones in tumor genesis and also in the modification of the natural history of experimental neoplasms In 1940 Huggins made history through his recognition of the fact that prostatic carcinoma in man is a hormone dependent tumor which can be significantly inhibited by depriving it of androgen through castration and the administration of estrogen The evidence for hormone dependence of carcinoma of the female breast is more tenuous and the results of modification of this dependence by castration the administration of androgens or of estrogens are less regular and satisfactory than in the case of prostatic cancer

Both androgens and estrogens have important general metabolic actions in addition to their more specific effects on the sexual organs and secondary sex characteristics These in sum account in large part for the therapeutic and toxic manifestations that are seen clinically Both the male and female sex hormones stimulate protein anabolism which is associated with an increase in appetite gain in weight and subjective improvement This effect of the hormones (usually more pronounced with the androgens than the estrogens) may be operative in a patient even when there is no inhibition of tumor growth Stimulation of osteoid formation is another action common to the androgens and estrogens This may also be an important nonspecific effect of the hormones in cancer therapy Estrogens stimulate squamous epithelium proliferation which must be helpful in the epithelization of ulcerating breast tumor lesions (See Chap 32 also Vol IV Chap 9)

Many attempts have been made to modify the steroid structures with the objective of retaining antitumor action while diminishing the effects on the sex organs Among the substitutes for testosterone propionate that have been studied extensively may be mentioned methyl androstenediol (Stenediol) and dihydrotestosterone (Stanolone) Stenediol is less androgenic and also less effective therapeutically Stanolone is not significantly less androgenic and the therapeutic results are equivalent to those of testosterone propionate Among the estrogens stilbestrol continues to be the agent of choice It is inexpensive active by mouth and potent No advantages have been demonstrated for the natural female sex hormones and the less estrogenic TACE (chlorotrianisene) is therapeutically inactive

The introduction of adrenal cortical steroid therapy for arthritis collagen diseases and as anti inflammatory agents was followed by the exploration of the value of these potent hormones in neoplastic disease With time the indications and limitations of cortisone therapy have been defined and at the present time the uses of this steroid together with its newer congener prednisone or Meticorten are clearly delineated

Urethane

Brief mention must be made of urethane a simple molecule that has been extensively studied because of its antitumor effects in certain neoplastic diseases of man Ethylcarbamate or urethane has thus far defied attempts to determine its mechanism of action Because of its resemblance to the amino acids it has been thought to be an antimetabolite evidence for this reasonable hypothesis however, has not been convincing Suffice it to say that this drug has limited but definite indications in the treatment of certain tumors Because of its relatively weak carcinostatic actions urethane will be replaced as soon as more effective agents become available In succeeding sections mention will be made of its clinical application in the treatment of chronic leukemias and multiple myeloma

CLINICAL APPLICATION OF DRUGS IN CANCER THERAPY

The administration of antitumor drugs in certain neoplastic diseases has contributed significantly to the over all medical care of the patient Careful and critical observations have demonstrated conclusively that objective regression of certain tumors can be achieved with the use of appropriate chemical agents In spite of the fact that in certain diseases it is possible to eradicate all clinical evidence of the neoplastic disease recurrence of tumor is inevitable and at the present time there is no

drug available that can cure any neoplasm This fact provides the basis for the first fundamental principle of cancer chemotherapy, namely that drugs are not indicated when the tumor apparently is localized to a single region Under these circumstances curative therapy by surgery or radiation must be offered to the patient

The drugs that have been described in the preceding section have definite indications contraindications limitations and decided toxicity The application of drugs to cancer therapy provides a useful adjunct to the physician which can benefit his patient a great deal it also requires an understanding of the natural history of the disease being treated and a knowledge of the clinical pharmacology and toxicity of the drugs to be used In the succeeding paragraphs the indications for the use of drugs in the treatment of a variety of malignant tumors will be presented in broad outline Greater detail covering clinical aspects of the diseases as well as their treatment will be found in appropriate chapters

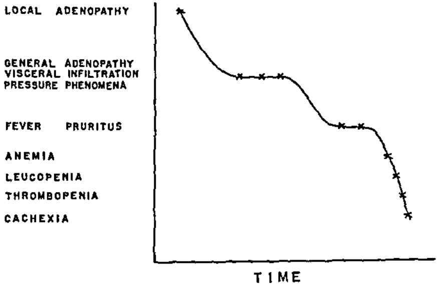


Fig 33 5 Schematic representation of the natural history of malignant lymphomas

The Lymphomas

Hodgkin s disease and the lymphosarcomas are included in the malignant lymphomas Although these diseases have many features that clearly separate them into distinct categories they also have many characteristics in their natural history that are common Figure 33 5 schematically depicts the natural history of the malignant lymphomas from the time of their clinically recognizable inception in a single focus, usually a lymph node to their extension to multiple nodes through the stage of widespread dissemination with constitutional manifestations such as anemia, fever, and pruritus to the terminal phase marked by cachexia and bone marrow exhaustion In the diagram the time scale has no units for in part the progression from the inception to the final stages of the disease is determined by the biologic characteristics of the tumor and, in part the time scale is influenced by the medical care given to the patient

From the introduction of this medical section it will be recalled that chemotherapy is not indicated when the disease is localized This is true in the case of the lymphomas as it is in all malignant tumors Evidence has recently been accumulated to demonstrate that vigorous therapy by radiation of malignant lymphomas which are clinically localized provides the patient with far better prognosis for 5 and 10 years than when the disease is not recognized or not treated until there is clinical evidence of extension [7] When the malignant lymphomas have become recognizably disseminated consideration can be given to the use of chemotherapeutic agents

Nitrogen mustard and many of its derivatives have been found to be particularly valu

able in the treatment of Hodgkin s disease at the stage where constitutional manifestations such as fever pruritus profound anorexia and asthenia are prominent Under such circum stances intravenous nitrogen mustard can be expected to produce remission of symptoms with evidence of tumor regression in 80 per cent of patients who have not been previously treated by chemotherapeutic agents There is tremendous variation in the duration of the remission which may be from 2 weeks to 6 months a median remission interval of 2 to 3 months is a reasonable estimate It must be recognized that nitrogen mustard has a small therapeutic index and hematopoietic depres sion occurs almost invariably with every course of the drug Because of this retreat ment should be spaced at intervals of two months minimum unless there are compelling reasons to disregard the hazard of additive toxicity to the bone marrow Frequently pa tients with Hodgkin s disease have constitu tional manifestations that are less acute than those mentioned above Under these circum stances chemotherapy may be undertaken on an ambulatory basis and the drugs of choice are triethylene melamine [16] or chlorambucil [5] The same proscriptions on retreatment with these drugs apply as with the intravenous nitrogen mustard A quantitative evaluation of the effect of nitrogen mustard and its deriva tives on the natural history of Hodgkin s dis ease has failed to demonstrate that these drugs have led to a prolongation of life [6] Evidence was accumulated however which showed that the use of chemotherapeutic agents decreased the frequency with which radiotherapy was re quired and maintained the patient in an asymptomatic state for longer periods than had been achieved before

Nitrogen mustard and its congeners are also indicated in the therapy of the lymphosar comas The histologic classification of the lymphosarcomas has important clinical impli cations since the natural history of the several types varies [7] The giant follicular lympho sarcoma is a relatively benign tumor and when it has become evidently disseminated chemo therapy may produce remissions that last for periods of from months to several years The small cell or lymphocytic lymphosarcoma and the large cell or reticulum cell lympho sarcoma have a more rapidly progressive course and their response to chemotherapeutic agents is also less satisfactory than in the case of the giant follicular lymphosarcoma Nitro gen mustard triethylene melamine triethyl enethiophosphoramide and chlorambucil have all been used in the treatment of the lympho-sarcomas The least satisfactory response can be anticipated in the reticulum cell lympho sarcoma that is in the phase of rapid progres sion Although the mustard compounds usu ally have some effect on the disease at this stage the remissions induced are very tran sient and the deleterious effect on the bone marrow usually outlasts the therapeutic effect on the tumor

There are two other indications for chemo therapy of the malignant lymphomas that are common both to Hodgkin s disease and to the lymphosarcomas It is not unusual for these tumors to involve the mediastinum with the production of the superior mediastinal com pression syndrome similarly these tumors may first appear as extradural masses that compress the spinal cord Since persistent pres sure in either of these two sites presents a serious and immediate threat efforts to re lieve the compression should be undertaken early In the past it was customary to insti tute radiotherapy Since the radiation reaction of vascular engorgement with localized edema presented the hazard of additional compres sion it was necessary to initiate treatment with very small doses and administer larger doses only when evidence of tumor shrinkage was apparent Since this could be dangerously time consuming it has been found helpful to utilize nitrogen mustard in superior medias tinal or spinal cord compression due to the lymphomas in order to produce a rapid shrink age of tumor The decrease in tumor size achieved by the drug is usually incomplete and it has been found advisable therefore to introduce radiotherapy at the time that the compression has been relieved by the mustard This combined therapeutic regimen reaches the desired end expeditiously and effectively

Anemia due to an increased rate of red cell destruction is a common manifestation of dis seminated lymphomas [14] This may be the most troublesome feature of the disease for considerable periods It has been found that

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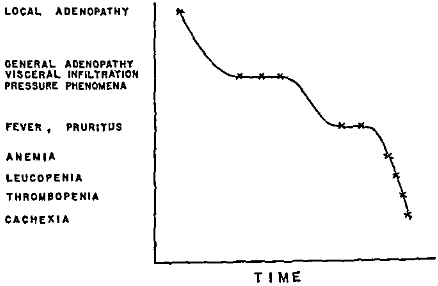

Fig 33 5 Schematic representation of the natural history of malignant lymphomas

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the administration of the adrenal cortical steroids can interfere with the process that leads to an increased rate of red cell destruction and thereby improve the anemia of the malignant lymphomas Cortisone or prednisone, is also indicated in the malignant lymphomas when the patient is symptomatic and cannot be treated by radiotherapy or chemotherapy owing to existing depression of bone marrow function with leukopenia thrombocytopenia or both The adrenal cortical steroids are able to abolish the constitutional manifestations while they are being administered When these drugs are discontinued there is prompt recurrence of the signs and symptoms and if they are continued for protracted periods the manifestations of disease will reappear, despite their administration Even though then cortisone and prednisone offer only a temporizing measure they may produce a necessary respite for return of bone marrow function so that further definitive therapy with radiation or the mustard compounds may be given

(See also Volume IX for a discussion of the chemotherapy of the lymphomas)

Leukemia

The treatment of leukemia has been revolutionized by the antitumor drugs Prior to the introduction of the folic acid antagonists in 1947 [4] only 5 of every 100 children with acute leukemia survived for one year An analysis in 1954 revealed that at that time 50 of every 100 children with acute leukemia survived for at least one year

ACUTE LEUKEMIA OF CHILDHOOD

There are three drugs available for the treatment of this disease the adrenal cortical steroids the folic acid antagonists and 6 mercaptopurine The selection of the drug depends upon previous treatment and also the severity of the manifestations of the disease at the time the treatment is to be initiated If the patient has received no previous treatment and is acutely ill with high temperature and bleeding manifestations the agent of choice is cortisone or prednisone The adrenal cortical steroids produce subjective and objective improvement in 60 to 70 per cent of patients and achieve this rapidly The remissions may be complete with restoration of the bone marrow to normal cellular characteristics or they may be partial with improvement in the peripheral blood, but persistence of blasts in the marrow in excess of 10 per cent When a remission has been achieved treatment should be continued at a lower dosage until there is exacerbation of symptoms Recurrence of signs and symptoms appears inevitably after a shorter or longer interval in spite of the fact that all clinical evidence of the disease may have been eradicated If the disease cannot be controlled by elevation of the adrenal cortical steroids to a higher dosage then it may be assumed that the leukemic cells have become resistant to these drugs and institution of another form of drug treatment is indicated

The folic acid antagonists are the drugs of second choice for the treatment of acute leukemia with systemic manifestations that appear to be an immediate threat to life These compounds are more toxic than cortisone or prednisone however in about half of the patients complete subjective and objective remissions can be achieved When this has been accomplished it is customary to discontinue the drug until exacerbation of the signs of acute leukemic process reappear It has been found that retreatment with this group of compounds is progressively less effective until ultimately the disease becomes entirely refractory

If in the estimation of the clinician the child with acute leukemia is not desperately ill and it is believed that a slower onset of action of drug effect will not seriously jeopardize the welfare of the patient then the drug of choice is 6 mercaptopurine (Purinethol) In 40 to 50 per cent of the patients 6 mercaptopurine achieved significant benefits after a lag period of from 15 to 21 days [2] It is customary to continue a maintenance dose of the compound after a remission has been achieved increasing this to full therapeutic levels when the peripheral blood or physical examination indicates exacerbation of the dyscrasia

It is to be noted that although each of the three compounds described in the preceding paragraphs is able to produce a complete hematologic and clinical remission of acute leukemia in children the development of re

sistance occurs with greater or lesser rapidity with each of them Fortunately cross resistance does not occur and therefore it is possible to switch from one drug to another when the refractory state develops It is this fact that accounts for the progressive prolongation of life that has been achieved in the past seven years

The importance of the development of drug resistance in cancer chemotherapy has led to intensive laboratory investigations that have developed fundamental concepts through brilliant experimentation [18] Evidence has been presented which strongly indicates that in every population of leukemic cells there exist mutants resistant to the chemotherapeutic agents that affect the majority of the cells The administration of an effective drug destroys the susceptible cells permitting with time the emergence of a population of resistant cells This process of selection is similar to that which leads to antibiotic resistance in certain microbial infections The mechanism just described does not indicate the fundamental biochemical characteristics of the resistant leukemic cells Exciting experiments have begun to uncover the secrets of these cells Thus it has been shown that one of the biochemical mechanisms of resistance is dependent upon the fact that there are multiple pathways of nucleic acid biosynthesis present within a cell A drug which interferes with one such biosynthetic pathway may have no influence on an alternative set of reactions that lead to the formation of the nucleic acids [19] In a particular instance of acute leukemia the majority of cells may be destroyed because the drug affects the more usual enzymatic reaction leading to the formation of nucleic acid A small portion of the cells however may be forming nucleic acid by an alternate pathway which is unaffected by the drug With the passage of time these latter cells at the outset in the minority will predominate since the drug administered has no inhibitory effect on their growth and multiplication These observations suggest that combination chemotherapy using drugs that would destroy all cells because they affect different fundamental cellular reactions would be more effective than any single drug This has been found to be true in experimental cancer chemotherapy of mouse leukemia however at the present time no combinations are available that have been found to be synergistic in the treatment of human neoplastic disease

ACUTE LEUKEMIA IN ADULTS

The antimetabolites methotrexate and 6 mercaptopurine have very limited success in the treatment of acute leukemia in adults Only 10 to 15 per cent of patients treated show improvement and usually this is observed in young adults

It has been customary in the past to administer cortisone to adults with acute leukemia as a means of providing symptomatic relief of the elevated temperature and also to decrease the purpuric manifestations that are so common in this blood dyscrasia Only very rarely did the adrenal cortical steroids produce objective evidence of hematologic remission In the past year and a half the availability of prednisone as well as the decreased cost of cortisone has permitted an attempt at therapy of adult acute leukemia using massive doses of these steroids It has been found that hematologic remissions can be achieved in 50 per cent of the patients using doses of 4 to 6 Gm daily of cortisone or 1 Gm daily of prednisone [24] Such tremendous doses of pharmacologically active steroids are not without hazard and the period of therapy must be compressed within a 10 day interval If remission is to be produced it occurs within this time The steroid is then decreased and discontinued The remissions are measured in terms of months and although retreatment may be successful the longest prolongation of life thus far observed has been 14 months Adrenal cortical steroid therapy of acute leukemia in adults can only be considered an opening gambit in this difficult therapeutic problem which will unquestionably be discarded when more effective drugs are available

CHRONIC MYELOID LEUKEMIA

During a large part of the natural history of chronic myeloid leukemia many therapeutic agents can produce remissions Splenic radiotherapy has long been the conventional approach and up to the present time no other means of treatment has been found that is qualitatively superior to it There are a num

ber of chemical agents that have also been found to produce remissions of this dyscrasia, such as arsenic in the form of Fowler's solution, urethane, nitrogen mustard, triethylene melamine and triethylenethiophosphoramide. Among the drugs, however, Myleran has rapidly achieved recognition as the most useful therapeutic compound [10–15]. This drug is effective by mouth, produces no unpleasant subjective side reactions, and induces remissions in 80 per cent of the patients treated, which last for periods of 2 to 48 months. When, however, the disease reaches the stage of the myeloblastic crisis, neither Myleran, any of the other drugs, nor radiotherapy can modify the course of the blood dyscrasia.

CHRONIC LYMPHATIC LEUKEMIA

This blood dyscrasia is characterized by protracted intervals during which it is completely asymptomatic. For this reason, and since no curative therapeutic procedures are available, it is customary to withhold treatment until the disease produces symptoms. When symptoms due to anemia, repeated infections, or pressure from enlarged nodes or visceral infiltration appear, therapy may be initiated with x-ray or with chemical agents. The drugs that have been found to be useful in this particular dyscrasia include nitrogen mustard and its derivatives. Triethylene melamine and the most recently introduced mustard, chlorambucil, have the widest application in the treatment of this blood dyscrasia. The latter has gained favor owing to the fact that, like triethylene melamine, it is active by mouth, but only very rarely produces nausea and vomiting. The therapeutic index is somewhat greater than that of triethylene melamine and although it produces bone marrow depression, it has been found safe to use even when the platelets are somewhat reduced. The determination of the amount and duration of therapy depends upon the response of the disease as measured by changes in the peripheral blood count and decrease in visceral and lymph node involvement. Available evidence indicates that approximately 50 per cent of the patients treated have significant objective and subjective improvement [31]. It is to be noted that this is less satisfactory than the chemotherapeutic treatment of chronic myeloid leukemia, but it has long been known that chronic lymphatic leukemia also responds less regularly and satisfactorily to radiotherapy than does the chronic myeloid form of the disease.

Multiple Myeloma

The introduction of paper electrophoresis of serum proteins as a routine laboratory examination in many clinics has led to the recognition of the pathognomonic myeloma protein with far greater frequency than had hitherto been appreciated [22]. This disease presents fascinating variations in its natural history, which include extensive skeletal involvement with pain, pathologic fractures, and hypercalcemia; predominantly neurologic involvement due to extradural cord compression or peripheral neuritis secondary to amyloid deposition, or compromise of renal function due to deposition of Bence Jones proteins within the nephron, leading ultimately to death due to uremia. Treatment of this disease is far from satisfactory, either with radiotherapy or the available chemotherapeutic agents. The greatest success has been reported from the use of a combination consisting of urethane and adrenal cortical steroids [23]. The latter have been found effective in decreasing the rate of red cell destruction and thereby ameliorating a common concomitant of the disease, namely, anemia. Evidence has been presented to demonstrate that urethane has a direct cytotoxic effect on the myeloma cells. One clinic has reported that 35 per cent of patients with this disease can be benefited by the use of this chemotherapeutic combination and that life is significantly prolonged over untreated controls [27]. (See also Vol. VIII, Chap. 18.)

Retinoblastoma

This relatively rare tumor is seen only in infants and small children. If recognized early, it frequently can be cured by enucleation. Unfortunately, the tumor frequently is multicentric in its origin and involves both eyes, either simultaneously or in succession. When the tumor is bilateral, or involves the eye after enucleation of one, it is customary to attempt to preserve vision by radiotherapy. Although radiation treatment of this tumor can cure a

high proportion of the cases the damage to cornea and lens produced by the high doses of x ray frequently leads to irreversible damage and blindness For this reason it was of great interest to note that nitrogen mustard can also produce a destructive effect on this tumor [17] More recently triethylene melamine given by mouth parenterally or intraarterially has been used in combination with radiation [25] The results reported indicate that the same end results can be achieved as with radiation alone but with a reduction of the x ray dose to levels that fail to cause damage of the normal ocular structure This constitutes a signal advance in the treatment of this tumor Parenthetically it should be noted that heredity plays an important part in the genesis of the retinoblastoma More than 80 per cent of the offspring of parents who have been cured of retinoblastoma develop this tumor For this reason the successfully treated patient should be warned against having children

Figure 33 6 summarizes the chemotherapeutic agents that are of use in the treatment of the lymphomas leukemias multiple myeloma and retinoblastoma (See Vol III Chap 33)

DISEASE	NITROGEN MUSTARD	TEM	CHLORAMBUCIL	Thio TEPA	MYLERAN	METHOTREXATE	6-MP	URETHANE	CORTISONE PREDNISONE
LEUKEMIA,									
acute childhood						●	●		●
acute, adult						○	○		●
Chronic lymphatic		●	●					○	
chronic myelocytic		○		○	●			○	
HODGKINS DISEASE	●	●	●	○					○
LYMPHOSARCOMA	●	●	●	○					○
MULTIPLE MYELOMA								●	●
RETINOBLASTOMA	●	●							

Fig 33-6 Tabular representation of the therapeutic applications of cancer chemotherapeutic agents in the treatment of the leukemias the malignant lymphomas multiple myeloma and retinoblastoma The solid dots indicate the drugs of first choice the open circles indicate drugs of second choice

CHEMOTHERAPY OF EPITHELIAL TUMORS

The epithelial tumors which include the adenocarcinomas statistically comprise a far larger proportion of all tumors than those which have been discussed in the preceding section With the exception of certain hormonal modifications that are of importance in the treatment of carcinoma of the prostate and breast few chemotherapeutic approaches of significant value have been developed It is nevertheless encouraging that a beginning has been made in certain other tumors and this will be mentioned briefly later

Carcinoma of the Prostate and Breast

The general principle that should be emphasized at the outset of a consideration of endocrine treatment of cancer is that hormones modify cellular mechanisms they do not produce new functions nor do they destroy existing functions This concept is important in recognizing the limitations of hormone therapy that are inherent in the mechanisms of action of these important biologic substances

It has been demonstrated clearly that the

epithelium of the prostate gland is dependent upon androgen for its normal growth, development and function A proportion of carcinomas of this gland estimated at approximately 65 per cent share many of the characteristics of normal prostatic epithelium including dependency upon androgen This is the basis for the androgen deprivation treatment of prostatic carcinoma that now is conventional and consists of castration together with the administration of estrogen [13] This regimen produces subjective and objective evidences of improvement and prolonged life [21]

There is one other tumor that has been found to be dependent upon androgen This is carcinoma of the male breast and the same therapeutic procedures used for carcinoma of the prostate produce significant remissions in the course of this tumor for protracted periods [30]

The evidence that carcinoma of the female breast is a hormonally dependent tumor is very much more tenuous It is true that the development of a carcinoma of the breast during pregnancy carries a very grave prognosis owing to apparent stimulation of the tumor Although this may well be due to estrogen stimulation it is also conceivably an expression of the increased vascularity of the gland during pregnancy which leads to a greater supply of nutrient to the tumor and increases the opportunities for generalized dissemination

It is well to recall that the background for hormonal therapy for carcinoma of the breast was laid by studies in experimental animals Thus Leo Loeb demonstrated that castration shortly after birth prevented the appearance of breast cancer in strains of mice with a high spontaneous incidence of the tumor Lacassagne showed that the protracted administration of estrogen to mice led to the development of breast cancer in a significant proportion of the animals even though the spontaneous incidence of the tumor was very low It was Lacassagne who suggested the possibility that androgen might be effective in the treatment of breast cancer Studies in his laboratory however failed to demonstrate any effect of the sex hormones on the course of breast cancer in mice after the tumor had appeared He also showed that hypophysectomy had no effect on the growth of the tumor if this ablative procedure was withheld until the cancer had made its appearance It is apparent, therefore that the administration of sex hormones or the use of various glandular ablative procedures in humans with carcinoma of the breast receive no particular encouragement from laboratory studies This in itself need not be a determining factor and it certainly has not curtailed the exploration of hormonal modification in carcinoma of the female breast

Castration and the administration of androgen in the premenopausal patient with widespread carcinoma of the female breast can be expected to produce evidences of objective tumor regression in from 15 to 20 per cent of patients and subjective improvement in a very much higher proportion of the cases In the patient who is three or more years postmenopausal it has been found that the administration of estrogen can cause tumor regression in perhaps as high as one third of the cases with again a higher frequency of subjective improvement [3] If estrogen is ineffective or causes an increased rate of tumor growth androgen should be tried in the postmenopausal patient At the present time there is a tremendous surge of interest in such procedures as adrenalectomy and hypophysectomy Consideration of the rationale indications contraindications limitations and results is beyond the scope of a discussion of chemotherapy It should be mentioned however that there is growing recognition of the fact that cortisone in small doses can also produce objective tumor regression as well as subjective improvement [20] This is of very great importance in the evaluation of adrenalectomy and hypophysectomy since cortisone is required in the postoperative maintenance of these patients

Bronchogenic Carcinoma

At the present time the soundest advice to give with regard to this tumor is that it is better to prevent it than to treat it Recognizing that this is more easily said than done mention should be made s
to treat ien it lo
cally r

radiation or when it has become widely disseminated One of the most distressing complications of bronchogenic carcinoma is extensive mediastinal infiltration by tumor with compression of the veins and other structures in the superior mediastinal compartment The therapeutic regimen that has been developed for this syndrome is the same that has been discussed for a comparable situation with the malignant lymphomas It consists of the administration of intravenous nitrogen mustard in order to achieve decrease in tumor involvement with relief of compression signs palliative radiotherapy follows The effect of nitrogen mustard and triethylene melamine on bronchogenic carcinoma is considerably less than their effect on the lymphomas For this reason the remissions produced by these drugs are usually transient In spite of this one clinic with great experience in the management of bronchogenic carcinoma recommends the routine use of the compound for the palliation of inoperable tumors that are too extensive for effective radiotherapy [11]

Carcinoma of the Ovary

There is a stage in the natural history of this tumor characterized by extensive peritoneal metastases and intractable ascites in which drugs may provide significant palliation It has been found that in approximately one third of these cases the administration of triethylene melamine or triethylenethiophosphoramide will lead to absorption of the ascites decrease in tumor mass and improvement in the general condition of the patient which persists for periods of from two months to as long as eighteen months [29] Unfortunately the protracted remissions are rare and the median symptom free interval is about four months

Serous Cavity Effusions

The involvement of the pleural pericardial and peritoneal cavities by tumor implant leading to effusions is a frequent complication of many neoplasms The introduction of radioactive colloidal gold and more recently of radioactive colloidal yttrium has been a valuable addition for the control of this troublesome and weakening phase of many cancers Because of the expense of the isotopes the cumbersome apparatus required to protect the professional personnel administering the solutions and the necessity to protect other patients in the vicinity of the one being treated the availability of a simple substitute has been welcome It has been demonstrated that nitrogen mustard administered intrapleurally can control effusions in 50 per cent of the cases irrespective of the type of primary tumor This is comparable with the results obtained with radioactive isotopes Although nitrogen mustard has been used intraperitoneally as well it would appear that triethylenethiophosphoramide is preferable for the local management of ascites or pericardial effusions because this drug produces significantly less intense local reaction [1] It must be recognized that the use of drugs or of radioactive colloidal isotopes in such situations constitutes symptomatic treatment which does not modify significantly the natural history of the underlying disease

Unsuccessful Attempts At CHEMOTHERAPY

Chemotherapeutic attempts have been made in many malignant neoplastic diseases with sufficient frequency so that it is possible to state certain negative conclusions With the drugs that are available for clinical use at the present time no significant value can be expected in the treatment of epithelial tumors arising in the upper respiratory tract stomach large intestine uterus or cervix Fibrosarcomas and primary bone tumors have also failed to be inhibited by the drugs that have been discussed in this chapter Specific mention should be made of the malignant melanoma and carcinoma of the pancreas Preliminary observations suggested that certain malignant melanomas responded to triethylenethiophosphoramide Further study failed to demonstrate an effect with sufficient regularity to warrant routine trial of this agent All the other compounds discussed have also been tried against malignant melanoma without significant effect A recent report suggested that the combination of nitrogen mustard with cortisone had an effect on the course of carcinoma of the pancreas The evidence was based on very limited experience and the *objective* improvement was poorly docu

mented Carcinoma of the pancreas has also been treated by alloxan and ethionine because of the known effect of these compounds on the pancreatic islets no therapeutic effects have been demonstrable

CANCER QUACKERY

A chapter on the principles of cancer chemotherapy would not be complete without mention of the fake medicines that are being foisted constantly on the gullible and anxious public It is paradoxical that this section of the chapter should be the appropriate place to set forth certain fundamental principles of cancer chemotherapy however, recognition of these basic tenets is of great aid in the evaluation of nostrums, as well as of legitimate drugs

Contrary to lay and professional opinion the clinical evaluation of cancer chemotherapy in man is extraordinarily difficult [8] A thorough knowledge of the natural courses of the malignant neoplasms being treated is essential for in many of these illnesses spontaneous and protracted remissions may occur Such episodes coincident with therapy may lead the inexperienced observer to entirely unwarranted conclusions It is well to recall that there is a considerable lag between the administration of radiotherapy and the clinically recognizable appearance of tumor regression On innumerable occasions patients have gone to a cancer quack shortly after the termination of radiotherapy and the improvement that occurred several weeks later was ascribed by the patient and the quack to the nostrum rather than to the x ray treatments

It also must be appreciated that most cancers produce a chronic rather than an acute disease Survival for many months after the clinical appearance of the terminal phase of the disease is the rule rather than the exception For this reason the mere persistence of life in the face of a hopelessly advanced cancer cannot be considered as positive evidence that the therapy being given at the time is of significance The fact that cancer is a chronic disease that kills slowly also means that eventually the patient realizes the diagnosis This leads to depression emotional instability and psychosomatic symptoms that complicate the clinical picture directly produced by the disease In such an environment psychotherapy finds receptive and responsive material It can be confidently anticipated that subjective improvement will follow the institution of any new form of treatment in a patient with advanced cancer, particularly if enthusiasm and optimism are part of the regimen Thus alleviation of pain is a singularly poor criterion on which to base a claim of efficacy for a cancer chemotherapeutic agent

The medical practitioner is finding it necessary with increasing frequency, to evaluate cancer treatments that are reported in the daily press *In his honesty, he may feel that an* important contribution has been made that he has missed in his hasty coverage of the medical literature For him it is well to recognize some of the earmarks of the fraudulent In the first place it is certain that when an important and significant advance in cancer chemotherapy is made every medical person in the world will know about it even though he never turns the page of a single medical journal Therefore if a patient asks him about a ' cancer cure with which he is unfamiliar *a priori* he can be confident that it is not of major import The allegation of the cancer quack that the medical profession will not recognize his cure because of vested interests is unmitigated nonsense Only the most ignorant or small of mind could ever be taken in by this paranoid cry A secret remedy is another clear mark of the fake No proprietary drug need ever be given serious consideration in cancer therapy It is self-evident that if any one person ever does discover a chemical compound, or combination of compounds which will cure any malignant tumor his fame and fortune are assured without the necessity of keeping his discovery a secret If it is necessary to look into an alleged cancer cure with more care attention should be focused on the documentation of the disease that has been cured A favorite trick of the quack is to diagnose as malignant a lesion that is inflammatory or otherwise self limited Under these circumstances his remedy cures cancer with dramatic success At the present time it is essential for cancer to be unequivocally documented by histopathologic sections before accepting the results of any therapeutic regimen The medical profession has an im

portant responsibility to prevent insofar as possible the perpetration of frauds on the laity In the field of cancer therapy this can best be done by examining hypercritically all reports on therapeutic procedures irrespective of the source of the claim

This completes an introductory statement on the current status of cancer chemotherapy This laboratory and clinical discipline is expanding daily and its impact will certainly be felt increasingly in the care of the patient with cancer

CHAPTER 34

The Care of Patients in the Incurable and Terminal Stages of Cancer

William E Howes

for it is impossible to make all the sick well "
(Book of Prognostics of Hippocrates)

Cancer rarely kills in a dramatic fashion but rather through slow deterioration The physician is wont to approach patients suffering from equally incurable diseases such as diabetes nephritis hypertension rheumatic endocarditis and coronary sclerosis with optimism but not so with cancer The sufferer, condemned before his doctor s pessimism is torn between the twin sirens of charlatanism and morphinism

Confronted with an incurable cancer sufferer the doctor should plan his strategy to maintain and support his patient (1) *to stay the further progress of the neoplastic growth* (2) *to supply general supportive measures* (3) *to care for complications that are bound to arise* and finally (4) *to make the patient as comfortable and contented as possible* Ultimate success in his management will depend as much on his humanitarian outlook as on his clinical insight

TO STAY FURTHER PROGRESS OF THE NEOPLASTIC GROWTH

Surgery irradiation and chemotherapy are the only modalities that can be called upon to stay further progress of the disease

SURGERY

The surgeon is justified in removing any neoplastic mass that causes pain or discomfort Such sidetracking procedures as gastrostomy gastroenterostomy cholecystojejunostomy colostomy etc frequently afford palliation Diversion of the urinary stream may result in regression in the size of primary bladder carcinoma

Castration in the male has a remarkably palliative effect though temporary in cases of carcinoma of the prostate [32] Castration in the female in the menstrual age suffering from mammary carcinoma has also resulted in remission of symptoms

Neurosurgical procedures may relieve intractable pain (Vol II Chaps 20 and 21)

RADIATION

In certain instances radiation therapy may prolong life reduce the size of neoplastic growths and relieve pain particularly when the tumor infiltrates nerves or when pain is caused by metastases to bone Irradiation may influence infection favorably and on occasion may control hemorrhage

CHEMOTHERAPY

For illustration of an example of co ordinated research for chemotherapeutic agents the reader is referred to *An Index of Tumor Chemotherapy* by Helen Dyer

Some of the drugs that have been shown to affect the tumor cell are briefly discussed

Arsenic

Arsenic in the form of Fowler s solution (potassium arsenite) has stood the test of time in the treatment of chronic leukemia

Dosage Liquor arsenitis min I t i d increase I min daily rechecking the white blood count at weekly intervals With response

the drug is stopped or may be decreased by a similar amount I min daily

Benzol

Benzol has been used in the past for the leukemias and lymphomas [12] Its action is however, unpredictable and dangerous Knowledge of its high toxicity as well as reported deaths in humans has lead to its having fallen into disrepute Newer chemotherapeutic agents have replaced it

Phenylhydrazine

This drug is effective in reducing the red blood cell count in polycythemia It is also extremely toxic and deaths following its use have been reported Hence it is seldom if ever used A preferable method of therapy is the use of P^{32}

Colloidal Lead

Lead orthophosphate $Pb_3(PO_4)_2$ was introduced by Bischoff as a compound of metallic lead suitable in stability and of less toxicity than metallic lead Both Ullman and Reynolds have reported beneficial results to cases treated by lead orthophosphate in conjunction with x ray and radium therapy An average of 30 cc of colloidal lead orthophosphate suspension containing 120 mg of lead is injected intravenously X ray therapy may be instituted some 3 days later Colloidal lead therapy is seldom used today

Coley s Toxin

This author has never observed a course of toxin therapy to have a beneficial effect

Nitrogen Mustard

This chemotherapeutic agent may bring about remission of fever and other toxic manifestations in ca es of generalized Hodgkin s disease It may bring about regressions in certain granulomatous and neoplastic masses reduce the size of the spleen and other tumor masses in cases of lymphosarcoma and leukemia [9] lower the white blood cell count in both lymphoid and myeloid leukemia as well as drop the red cell count in polycythemia The recommended dose is 0 1 mg per kg of the patient s body weight Daily injections of nitrogen mustard for 3 or 4 days comprise the usual course of treament or the total dose may be given at one time

Certain chemical derivatives of nitrogen mustard such as triethylenemelamine (TEM) triethylenephosphoramide (TEPA) and others are utilized with minor advantages over the nitrogen mustard (see Chap 33)

Urethane

Urethane (ethyl carbamate) affects cellular proliferation probably as an inhibitor of nuclear division Temporary remissions have been reported in treatment of myelogenous leukemia [44] metastatic anaplastic carcinoma [29] and prostatic carcinoma [33] Its best effect is in the treatment of myloma and chronic myelogenous leukemia a fall in the total leukocyte count results from the accelerated maturation of the circulating leukocytes [38] Webster reports 2 fatalities after treatment with urethane in myelogenous leukemia

Dosage 1 Gm enteric capsule t i d for 10 to 20 consecutive days under observation

Stilbamidine

Snapper has reported temporary improvement in patients suffering with multiple myeloma (Vol VIII Chap 18)

Folic Acid Antagonists

Beneficial effects of folic acid antagonists occur in patients with leukemias and other forms of incurable cancer Aminopterin (pteryglutamic acid) one of the so called folic acid antagonists has been purported to induce remissions in acute leukemia [60] The maintenance dose of aminopterin is 0 5 to 1 0 mg daily (Chap 33)

HORMONAL THERAPY

a Estrogens and androgens produce marked palliation in certain instances

b Cortisone and pituitary adrenocorticotropic hormone (ACTH) are powerful hormonal substances They produce striking but temporary shrinkage of enlarged lymph nodes spleens and livers in patients with chronic lymphatic leukemia and acute leukemia as well as slight shrinkage of lymph nodes and spleen of patients with Hodgkin s disease These hormones a'so produce a sense of well being (Chap 32)

GENERAL SUPPORTIVE MEASURES

The advanced cancer patient has as a rule been ill for a very long time In all probability there is *(a)* weight loss *(b)* anemia *(c)* vitamin deficiency, *(d)* pain with coincident loss of sleep and appetite, all of which will add to the restless nervous exhausted state In time weakness and disability will prostrate the individual while *(e)* dependent edema which may indicate a lowered blood protein level will make its appearance In addition the advanced cancer patient is subject to a host of disturbing symptoms He is frequently troubled with *(f)* cough, *(g)* disturbance of bowel habits as manifested by diarrhea or constipation *(h)* vomiting and *(i)* other upper abdominal complaints Because of his debilitation he is more prone to *(j)* infections and *(k)* various bleeding phenomena These should be treated by suitable replacement therapy

Pain is a constant companion of advanced cancer and is often the most difficult symptom to control Every effort should be made to analyze the cause of pain It is conceivable that on occasion pain may actually be due to a psychic phenomenon secondary to the patient s unwillingness to accept the situation As a rule however there is definite morbid anatomy causing the suffering Pain attributable to several causes may be experienced by the patient with advanced pelvic cancer To prescribe narcotics without determining the exact cause of pain may disguise a complication that treatment can relieve For example, pain due to pyometria can be concealed with opiates but a more efficacious treatment would be to dilate the cervical canal and institute uterine drainage

No matter what the etiologic pain factor may be the sufferer is in need of reassurance An atmosphere of despondency should not be apparent in the sickroom

The following conditions are itemized as possible sources of pain with particular methods to combat pain suggested in each instance

Any ulceration on the surface of the body will cause pain Dressings should be changed frequently Bacterial flora can be changed by sprinkling sugar over the ulcerated surface or by adding acetic acid to the wet dressing In the presence of infection wet dressings of boric acid magnesium sulfate aluminum acetate, saline, or alcohol 50 per cent are suggested If the above solutions appear to irritate carbolic acid up to 0 5 per cent may be added If the ulceration is walled off and the infection minimal such ointments as Aquaphor, petrolatum jelly lanolin boric *acid cod liver oil allantoin nitrofurazone* may be tried Carbolic acid up to 0 5 per cent may be added to any of the above ointments Nupercainal 1 per cent or benzocaine 3 per cent ointment may be needed to anesthetize the ulcerated surface When such an ulceration becomes chronic with no tendency to epithelization a more stimulating ointment is indicated such as scarlet R 5 per cent or Radon ointment or preferably Thorium X in a petrolatum jelly 150 to 300 uc per cc

Pain from any open sore in the mouth can be partially alleviated by such hygienic measures as saline aspirin or weak peroxide mouth washes The agonizing nature of open sores in the mouth may prevent persons who have them from taking adequate nourishment Such patients are best placed on a soft or liquid diet or it may be necessary to tube feed them Specially prepared throat lozenges or a solution of aspirin (5 to 6 tablets dissolved in ⅓ glass of water) will often bring about temporary relief One per cent Butyn sulfate or in unusual instances, a solution of 0 5 per cent cocaine hydrochloride may be sprayed in the mouth before meals Along with these topical applicants it is well to prescribe codeine sulfate gr 0 5 q 3 h Since the pain is accentuated by local infection antibiotics should be prescribed Radionecrosis is extremely painful and a simple excision or debridement will result in almost instantaneous relief

Infection extending posteriorly into the contents of the pterygoid fossa will produce trismus Small doses of x ray to cross fire at the pterygoid fossa plus antibiotics may bring relief

Pain may be referred to the ear from any ulcerating intraoral cancer This is usually a symptom of advancing disease but it may also accompany a severe radiation reaction Irrigation of the mouth and the external auditory canal with warm saline may help if not an

icebag should be tried If the affection is secondary to an eustachitis nose drops such as ephedrine sulfate 1 per cent or Neosynephrine 0 25 per cent will aid Codeine and aspirin should be prescribed before resorting to opiates

Intraoral ulcerations quickly extend to bone with development of an osteomyelitis to add an additional pain factor Osteomyelitis of the mandible in conjunction with cancer especially when it occurs postradiation can rarely be checked In such instances a partial removal of the mandible is indicated The hemimandible is best removed through the mouth to prevent distressing salivary fistula

When the bone is not involved the mandibular nerve may be injected with alcohol Intramedullary section of the 5th and 9th nerves in suitable instances (uncontrolled cancer of the floor of the mouth and tongue) will result in dramatic relief of pain There is however a coincident complete anesthesia of the tongue and buccal mucosa on one side which may give distressing symptoms

Backache is a common complaint among bedridden cancer patients Such patients can be helped by the use of a firm foam rubber mattress supplemented with massage and diathermy Too often continued backache is due to hidden metastases in the bodies or pedicles of the vertebrae If the cause be due to hydronephrosis institution of adequate urinary drainage or nephrectomy will bring relief Pelvic infection may be relieved by surgical drainage along with antibiotics The relief that simple sitz baths may give must not be forgotten If the neoplastic involvement extends to nerve roots and no relief is obtained by radiation therapy a neurosurgical procedure may be indicated X radiation alone can often relieve the continuous aching pain caused by the presence of a retroperitoneal tumor

Pain will result from spread through the pelvis of carcinoma arising in the cervix uteri Such a spread of uterine cervical cancer very early extends around and chokes off the ureters with resultant hydropyonephrosis If this process is unilateral nephrectomy is advantageous—this even though incurable carcinoma is known to exist within the pelvis [19] Transplantation of one or both ureters to bowel is at present in vogue and when successful, this procedure is of real palliative value In the most advanced cases nephrostomy or at best transplantation of ureters to skin may be all that can be done Pelvic infection may complicate treatment of carcinoma in the female pelvis To remove a pus tube to dilate the cervical canal for drainage of a pyometria or to incise and drain a pelvic or retroperitoneal abscess may bring relief

Constipation usually accompanies any chronic debilitating disease With lack of exercise and fresh air with vitamin B deficiency with narcosis and resultant loss of muscle tone constipation can hardly be prevented The patient must be allowed bathroom privileges as long as possible Fresh fruits and vegetables should be a part of the daily diet Adequate ingestion of water is important and regularity should be encouraged Saline laxatives magnesium sulfate and sodium phosphate are the preferred ones Mineral oil may be given by mouth although this has the disadvantage of leakage and robbing the system of needed vitamin A Psyllium seeds have none of the disadvantages of mineral oil they swell in the digestive tract and serve as a normal bulky peristaltic stimulant *Dosage* One tablespoonful followed by water morning and night

Patients should be helped to stool after breakfast and dinner Should voluntary effort fail low tap water or saline enemas my be given every second day Glycerine or soap suppositories may at times be preferable to enemas With more severe constipation it is best to precede the tap water enema with a retentive oil enema—250 to 500 cc of mineral oil is instilled to be retained if possible for halt an hour At times the dried out fecal mass may be softened by irrigating with a two way rectal tube using warm tap water a small amount of hydrogen peroxide to the pint of water will be efficacious An oil retentive enema of 1 pint followed by a hot soapsuds enema of approximately 2 quarts is usually more successful Doxinate a wetting agent consisting of dioctyl sodium sulfosuccinate is efficacious in softening impacted fecal masses Manual removal must be carried out if the above procedures are unsuccessful

Diarrhea may result from a carcinoma located anywhere along the intestinal tract or

be due to peritoneal implants as well as radiation injuries When the stools are frothy and fetid the possibility of sprue secondary to anemia or pancreatic disease must not be forgotten Treatment should be directed to the basic cause It may be necessary to place the patient on a fluid diet or withhold food entirely The patient can be sustained temporarily on parenteral fluids Milk of bismuth kaolin and pectin may give relief A tap water enema should always be given early to clean out the lower bowel If the diarrhea continues unabated paregoric and morphine may have to be resorted to A sidetracking operation may relieve an otherwise intractable diarrhea caused by an obstructing inoperable neoplasm

Vomiting may be due to intestinal obstruction the obstructing site may be anywhere from pylorus to upper rectum The location of obstruction should be determined and when the growth is not removable relief should be given by various procedures depending partially upon the site of obstruction When possible an intestinal sidetracking procedure should be attempted, if not an enterostomy may be performed

Vomiting may be secondary to liver or pancreatic involvement Here but minimal palliation can be expected Frequent gastric lavages are recommended along with parenteral fluids to support the patient With persistence of the vomiting all food by mouth should be discontinued Fluids salt sugar and proteins can be supplied by intravenous route Gastric lavage followed by a Wangensteen type of drainage may be necessary Sedation such as phenobarbital sodium gr 2 by hypodermic will reduce nervous irritability A complicating acidosis or nephritis may also bring on vomiting Here therapy must be directed to the underlying etiology

Sensitivity to opiates should not be forgotten as a frequent cause of nausea and vomiting Symptoms of dyspepsia biliousness epigastralgia etc may result from concomitant gastroduodenal or gallbladder disease as well as from the presence of neoplasm anywhere throughout the length of the gastrointestinal tract and from secondary invasion of liver or spread onto peritoneal surfaces Until the exact cause of complaint is identified the following drugs may be tried to give relief

Aluminum hydroxide	ZI—II
Sodium bicarbonate	gr 10—t i d p r n
Atropine	gr 1/100—t i d a c
Syntropan	50 mg—t i d
Phenobarbital	gr 0 5—1 5

COMPLICATIONS DUE TO CONCOMITANT DISEASE

Tertiary syphilis appears on the cancer wards in from 5 to 10 per cent of all admissions Present methods of treatment with antibiotics (penicillin) is indicated not in lieu of cancer therapy but in conjunction with cancer therapy

Tuberculosis A routine chest x ray of the cancer patient may bring to light the presence of a chronic fibroid phthisis unsuspected up to the moment Every effort should be made to treat the tuberculous lesion independent of the cancer process When possible open cavities should be compressed by accepted surgical methods or where surgery is contraindicated, streptomycin therapy should be carried out

Herpes zoster also comes as a frequent visitor to the cancer ward It commonly attacks the leukemic individual Susceptibility to this infection is in some way increased by debility Sudden onset of neuritic pain often about the trunk or thighs should lead the attending physician to consider the possibility of an incipient herpetic eruption A slight T rise may be among the prodromal symptoms Moderate doses of x ray to both the skin regions involved and the cord segments supplying the affected part tend to abort the process as well as dampen the pain almost immediately

Herpes simplex (fever blisters) may appear on the lips and about the mouth of the cancer patient the condition is associated with debility and secondary infection The following are suggested as local applications

R/ Spiritus camphorae 15 00 ZZ/SS
 Sig Local application
R/ Solutionis zinci sulphatis 2 per cent *15 00* ZZ/SS
 Sig Local application
R/ Tincturae benzoini compositae 15 00 ZZ/SS
 Sig Apply locally allow to dry

Pleurisy with or without effusion in the

cancer patient usually indicates metastatic spread to the pleural surface X ray of the chest after drainage of the fluid accumulation and when indicated injection of air into the pleural space to drop the lung away from the parietal pleura may help in making an exact diagnosis Effusion secondary to a shower of pulmonary infarcts in case of endocarditis must be differentiated from effusion due to metastasis, a blood culture is required Endo carditis and pneumonia will need to be treated according to prescribed methods

Ascites is usually indicative of peritoneal or retroperitoneal metastases Repeated courses of radiation therapy may bring relief Here the use of radiogold is in the experimental stage and offers some promise Rarely such a patient will respond to a mercurial diuretic such as Mercuhydrin 1 to 2 cc intravenously

Myocardial degeneration valvular heart disease and *coronary disease* are common entities among older people The cardiac status is often the factor deciding whether that individual may be expected to withstand radical surgery

PAIN RELIEVING AND TRANQUILIZING DRUGS

SOPORIFICS

The barbiturates tend to allay nervous apprehension and thus induce sleep Pheno barbital gr 1 5 to 3 is the basic medicament With tolerance or allergy it may be necessary to turn to such other drugs as chloral hydrate 0 6 Gm to 2 0 Gm diluted in water or in milk With extreme restlessness it may be nec essary to use paraldehyde 4 cc with cracked ice or icewater this dose can be increased from 8 to 12 cc by rectum Paraldehyde can also be given by hypodermic Bromides are useful drugs that have a helpful sedative ac tion Because many do not tolerate bromides well and there is always danger of skin manifestations they are not prescribed as frequently as the barbiturates *Dosage* Sodium bromide or triple bromide gr 15 as needed

ANALGESICS GENERAL

Drugs helpful for relief of pain can be separated into such coal tar derivatives as acetanilid and phenacetin and the salicylic acid derivatives of which aspirin is best known as well as the narcotics

Acetylsalicylic acid (aspirin) gr 10 every 3 hours as needed will usually be sufficient to lower the patient s pain threshold so as to allow him to carry on in relative comfort for months without necessity of reverting to stronger habit forming drugs At times the benefit can be heightened by combining aspirin with phenacetin and caffeine

Cobra venom consists of a solution of the cobra venom toxin Its effect is supposedly cumulative and it is therefore given at daily intervals in a series of injections dose 10 to 30 min 1 to 2 cc by hypodermic In the author s experience this drug in nontoxic amounts effects but minimal pain relief

NARCOTIC DRUGS

Codeine is the least harmful and most use ful of all narcotic drugs To relieve a racking cough (0 1 to 0 25 gr) it is almost specific Codeine is even more valuable to obtain re lief of pain (0 5 gr) When given in con junction with aspirin there appears to be a heightening of the effect 0 5 gr codeine plus 5 or 10 gr of aspirin every 3 or 4 hours as needed On occasion less gastric disturbance may result by alternating codeine with the aspirin Seldom is it useful to increase the individual dose of codeine over 1 gr When tolerance has been raised above this level it is advantageous to switch to some other opium derivative

Dover s powders 0 3 Gm to gr 5 in capsule alone or with aspirin will often give relief when the tolerance to codeine has risen

Pantopon hydrochloride is composed of all the alkaloids of opium in the form of a hydro chloride Pantopon retains all the pain reliev ing factors of opium while it is purported to have fewer side effects It is supposedly less habit forming than morphine *Dosage* 1/6 gr to 1/3 gr

Dihydromorphine hydrochloride (Dilaudid hydrochloride NNR) is an effective nar cotic This drug has fewer side effects on the gastrointestinal tract than morphine but it is a known depressant to the respiratory center It may also produce skin rash and certain other sensitization phenomena In the author s experience there is a marked individual varia tion in the effect of this drug *Dosage* 1/64 gr by mouth 1/3 gr by hypodermic

There have been many favorable reports about meperdine hydrochloride (Demerol hydrochloride NNR), a morphine derivative. It is supposed to be less habit forming and less apt to build up a tolerance than other opiates. There is, however a marked variation in its effectiveness on different individuals. *Dosage* 0.05 to 0.1 Gm.

Methyl dihydromorphinone hydrochloride (metopon hydrochloride), Sharp and Dohme is a morphine derivative. It is purported to have double the analgesic effect of morphine with a duration of action equal to morphine. It has no emitic action while tolerance is built up more slowly than with morphine. *Dose by mouth* 6.0 to 9.0 mg repeat with recurrence of pain.

Methadone hydrochloride (methadon) Parke Davis and Company is a new synthetic organic compound found to have a pronounced effect in controlling pain—parenteral dose 2.5 to 10 mg. Methadon and its isomers have been reported upon by Denton and Beecher [17] as being effective for the relief of postoperative pain.

Heroin (diacetylmorphine hydrochloride) is notably habit forming and is no longer listed in the National Formulary. It has no particular advantage over other narcotic drugs listed above.

Opium is the source of all narcotics and from which all alkaloids are separated. At the present time it is used only in the form of suppository 1 gr per suppository. There are many instances when opium suppositories will be found efficacious, as when the patient is unable to tolerate narcotics by mouth.

Morphine is the principal alkaloid of opium and has stood the test of time as the most efficient narcotic to bring relief to the more advanced cancer patient. It is rarely given by mouth. It is more efficient when given sub-

TABLE 34–1.—SUMMARY OF THE CLINICAL USE OF TRANQUILIZING (ATARACTIC) AGENTS

Type of illness	*Drug of choice for initial treatment*	*Recommended dosage*	*Route of administration*
Psychoneurotic Anxiety tension state	Phenobarbital. If no improvement meprobamate	30–60 mg t.i.d. or q.i.d. 400 mg daily to 600 q.i.d.	Orally Orally
Acute Situational Reaction Severe agitation emotional lability aggravation of preexisting psychoneurosis. Reaction to presence of cancer or to certain therapeutic procedures (colostomy excision of portion of face amputation etc.)	Chlorpromazine	25–50 mg (may repeat if necessary) 25 mg (may repeat if necessary after 45 min.–1 hr.)	Orally Intramuscularly
Acute Psychotic Reaction Suicide attempt agitation confusion	Chlorpromazine Promazine	As determined by individual situation	
Alcoholic Syndromes Subacute withdrawal phase	Meprobamate	Titrate 400–600 mg b.i.d. t.i.d. q.i.d.	Orally
Acute hallucinosis and delirium tremens	Chlorpromazine Promazine	As determined by individual situation	
Miscellaneous Drug addiction withdrawal phase	Promazine		
Incurable Cancer	Any combination of ataractic agents depending on the clinical situation		

After J. H. Moyer, K. Pevey and V. Kinross Wright, *GP 15* 97 1957

cutaneously, 0 25 gr repeated as needed As stated tolerance to this drug is rapidly built up and therefore the dose must be increased to render necessary relief

TRANQUILLITY (ATARACTIC) AGENTS

Table 34 1 summarizes some of the clinical applications of certain ataractic agents It indicates their possible role in controlling various types of reactions of patients to the presence of cancer or to certain therapeutic procedures in the treatment of cancer (amputations etc) as well as their role in conjunction with narcotics and other medications in aiding to control symptoms in patients with incurable cancer

ADDENDUM EUTHANASIA

Norman Treves

The administration of sedatives and narcotics to patients brings up discussion that has recurred in medical practice since the early part of the seventeenth century It has been felt by many members of the profession that once the terminal stage of cancer has been reached narcotics in large doses should be indiscriminately administered But since the life of the incurable cancer patient is usually of long duration sedatives hypnotics and analgesics should be used with utmost caution

Euthanasia literally means a good death (a gentle death of little suffering) There is little to be found in medical writing on the management of the dying or on the treatment best adapted to the relief of suffering incidental to that condition Since the subject is not taught in any of our medical schools the physician enters practice having to learn for himself what to do and what not to do in the most solemn and delicate position in which he can be placed—in attendance on the dying It is for him to administer the resources of medical art in aid of an easy gentle and placid death The whole subject of euthanasia or of a calm and easy death insofar as it respects the physician is in need of special study

The word *euthanasia* refers to two things first the practice of painlessly putting to death those suffering from distressing symptoms as an act of mercy second the practice of relieving suffering so that death will take place with as little distress and pain as possible These are such totally different aspects that each should be considered separately

The State has never sanctioned the first and the physician is not given the right by any diploma he possesses to administer a drug to cause death It is probable that even if it were permitted the majority of doctors would refuse to do so since they enter their profession to maintain and prolong life not to take it

Euthanasia is a matter of interest to all for death sometimes comes very slowly and delay may be tragic to the patient and those around him A physician is permitted to give drugs to relieve pain and suffering so that life may go on with as little disturbance as possible and death may take place briefly He may give as much medicine as he thinks a particular patient needs provided the aim is to relieve symptoms He must be guided by what is the best interest of the patient But however much death might be desired by the patient in no circumstances is a medical man ever permitted to hasten its approach It must not be assumed that the administration of drugs to relieve suffering necessarily hastens the end for if the pain persists it will soon undermine the health and even if a drug has a depressing action its harmfulness may be more than counterbalanced by the serious effect of the prolonged suffering and pain that it is given to relieve Up to the present the State has entrusted to the medical profession a tremendous power in regard to this aspect of euthanasia not so much by establishing laws to enable its members to act but by not establishing laws that limit their power

Now that many drugs are available for relieving pain no patient should reach the stage when he desires an operation in the hope that it may lead to death nor should he be allowed to linger on in agony with his pain unrelieved Unfortunately it is still difficult when life is likely to last for years to counteract pain all the time for if drugs are administered over a long period they may eventually fail to act or may lead to demoralization which ultimately may be as distressing to the patient and his friends as severe pain

Death from old age—the natural termina

tion of life and the simplest form of death that can occur—creeps on by slow and almost imperceptible degrees It is characterized by a gradual and proportionate decay of all the functions and organs of the body and as a rule it presents no symptoms that call for special treatment It is only when the normal course of decay is disturbed by supervening disorder or disease of an important organ or by surrounding circumstances that suffering of any kind attends it Good nursing and the due administration of light food and stimu lants comprise all that is needed The approaches to death are so gentle and the act of dying so easy that nature herself provides a perfect euthanasia

CHAPTER 35

Special Nursing Problems of the Patient with Cancer

Mary G Patterson

The patient who suspects or knows he has a cancer is frightened by a threat to which he can attribute no cause The nurse needs to understand that the fear of cancer anesthesia operation mutilation dependence pain and death may be expressed in hostility querulousness demands aggressive and destructive behavior, or withdrawal depression and rejection The nurse is the mother figure and guilt and blame will be childishly placed on her shoulders She must be very sure of her own feelings She may be causing the patient unnecessary hardship by expressing in similar patterns her own inability to accept the situation An objective and balanced view of the problem must be maintained She cannot permit her judgment to be clouded by personal identification with the patient or self projection into his situation With all this she must attempt to be receptive pleasant calm firm sympathetic reasonable and understanding She must be a good listener realizing that the patient gets relief when he is allowed to express his feelings But she must be able to judge at what point the emotional disturbance becomes pathologic so that special treatment is required and this observation should be reflected in her notes She must reassure the patient by instilling trust hope and security through her technical competence confidence in the doctor and support of the value of the treatment and the outcome She must never neglect reject abandon or punish a patient irrespective of the sight sound or smell of him It is her job to succor him to the end

Special oncologic nursing care due to the nature of tumor growth results from two main problems The one is obstruction which interferes with essential functions in the gastrointestinal tract genitourinary tract respiratory system circulatory system etc The other is ulceration of the tumor onto a tissue surface or erosion of a blood vessel complicated by infection necrosis hemorrhage drainage odors pain anemia etc Nursing care related to treatment includes management and rehabilitation of the patient with a surgical defect management of patients receiving chemicals hormones toxins viruses and other experimental agents and management of radioactive materials

NURSING CARE OF PATIENTS WITH GASTROINTESTINAL CANCER

Obstruction of the lumen of the gastrointestinal tract is one of the commonest problems To stimulate the patient s appetite and raise his morale the food may be served in its usual form and then liquefied with a Foley Food Mill or an electric food liquefier such as the Waring Blendor Baby foods available can also be used The patient with feeding ostomies should sit up and participate as much as possible in the feeding procedure He should remain sitting or be supported in Fowler s position unless contraindicated for about an hour after feeding to prevent spilling This is important to remember with older people who like to lie down after meals A glass of water should be given with each feeding The surrounding tissue may be protected with soybean powder dissolved in enough

water to make a thick paste aluminum paste, aluminum powder sprinkled on the skin or zinc peroxide paste with aluminum powder

Resection of esophageal tumors produces a variety of special postoperative problems If the cervical esophagus is resected, then the patient must feed himself through the stoma above the clavicle and needs a *mirror* add d to his equipment If the larynx has been re sected with the esophagus it is vital to have the tracheal opening carefully labeled "do not feed since the external appearance of each stoma is similar

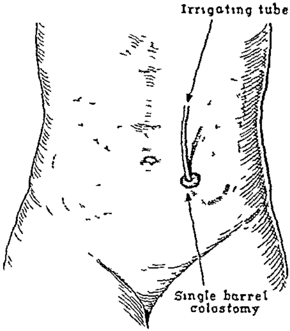


Fig 35 1 Irrigating the funct oning colon

The central problems in nursing care of the patient whose tumor is in the *colon* or *rectum* revolve around preparing those organs for surgery and the postoperative manage ment of the colostomy

The main nursing problems are to watch for hemorrhage signs of pocketed material phlebitis and fistula Irrigations of the poste rior wound may be done with the patient in knee chest position (see Figure 35 2) This position allows the bladder to fall normally in the pelvis and promotes recovery from operative trauma Early ambulation of pa tients with perineal wounds presents the prob lem of keeping the dressing in place while the patient is active It has been found that the

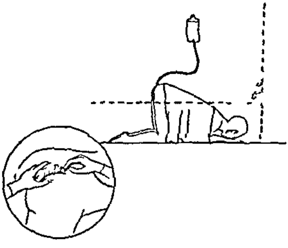


Fig 35-2 Posterior wound irrigation

Patterson pelvic binder (see Figure 35 3) keeps the dressing secure and gives the patient more confidence in moving about

NURSING PROBLEMS OF PATIENTS WITH CANCER OF THE GENITOURINARY SYSTEM

Basic objectives are prevention of infec tion maintenance of free urinary drainage and the control and management of urinary output Catheterization and irrigation of the bladder measurement of residual urine the psychologic and physical stimulation of void ing are part of routine management The last should be attempted at a reasonable hour after known adequate intake when the patient is up and about and if possible in the bath room Various suggestive devices such as run ning water glass of water to drink pitcher douche cool compress to the pubic region etc can be used to induce voiding The in dwelling catheter usually drains into a cov

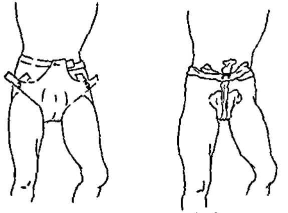


Fig 35 3 Patterson pelvic binder

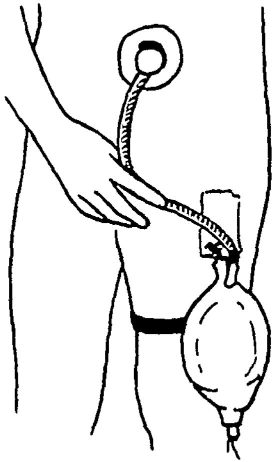


Fig 35 4 Leg urinal used here with suprapubic cystostomy tube

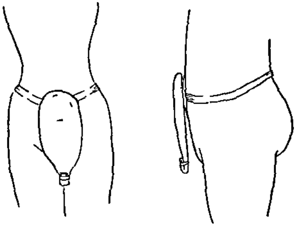


Fig 35 5 Pierce bag for manag ment of the *wet colostomy*

ered gallon jug at the bedside If the patient must wear the catheter home a leg urinal may be used A suprapubic cystostomy tube may usually be managed in a similar manner (Figure 35 4)

Special nursing problems result from the diversion of the urinary stream because of obstruction or surgical interference One or both ureters may be implanted into the colon In this case the urinary and fecal secretions are collected in and expelled from the rectum These patients are incontinent for a period of time and only gradually does sphincter control return Care of the perineal skin is very important It may be several months before the need to use the bathroom in periods as long as 3 5 hour intervals can be established This factor determines rapidity of rehabilitation of the patient These patients should be instructed not to take an enema or any other treatment which may produce an ascending infection of the urinary tract by forcing the rectal contents into the implanted ureters

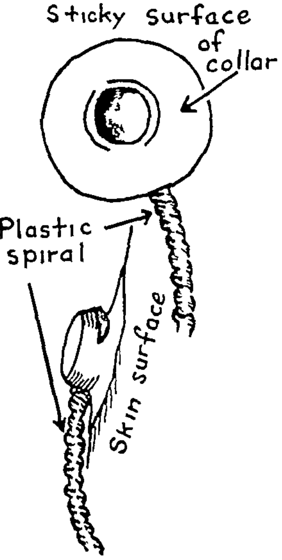
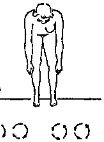


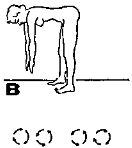
Fig 35 6 Singer cup for management of cutaneous ureterostomy

A



Stand with feet 8 apart
Bend forward from the waist
Allow arms to hang toward the floor by gravity
Relax
In rhythm
- Loosely swing both arms in a circl clockwise
- Loosely swing both arms in a circle counter clockwise
- Loosely swing each arm in oppos te directions—outwards
- Loosely swing each arm in opposite directions—inwards
- Stand and allow arms to fall to sides

B



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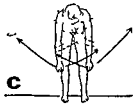
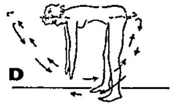


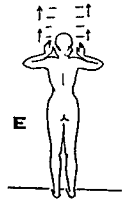
Stand with feet 8 apart
Bend forward from the waist allowing arms to hang toward the floor by gravity
Swing both arms together describing an arc from one shoulder to the other
Do not bend elbows
Stand allow arms to fall to side

D



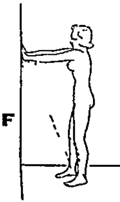
Stand with feet 8" apart
Bend forward from the waist allowing arms to hang toward the floor by gravity
In rhythm
- Swing both arms together describing an arc from over head to hip
- Swing each arm in opposite directions describing an arc from over head to hip
- Stand and allow arms to fall to side

E



Facing the wall and with toes touching it stand against it with feet 8" apart
Banding the elbows place palms against the wall at shoulder level
Work the hands up the wall parallel to each other unt l fully extended
(Mark the wall each day at height reached to measure progress)
Work hands down to shoulder level
Repeat

F



S and fac ng the wall at arm s length with feet 8" apart
Place hands against the wall at shoulder level parallel to each other
Slowly flex the elbow bending the trunk forward unt l forehead touches wall
Straighten elbows slowly until body is upright
Repeat
Note: Keep head trunk and legs in straight l ne

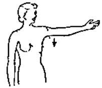
G

Stand at right angle to the wall with affected arm next to the wall
Place palm against the wall at shoulder level
Work the hand up the wall unt l fully extended
Work hand down to shoulder level
Repeat

H

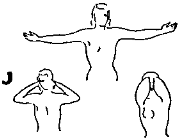
Stand w th feet 8 apart
In rhythm
Extend arms sideways to shoulder level
Flex elbows touching fingers at nape of neck
Extend arms sideways to shoulder level
Flex elbows touching fingers at back of waist
Repeat

I



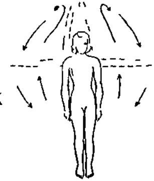
Stand with feet 8 apart
Extend affected arm sideways to shoulder level
In rhythm
Moving the arm forward flex elbow placing hand on opposite shoulder
Lower elbow against body
Raise elbow to shoulder level
Extend arm sideways to shoulder level
Repeat

J



Stand with feet 8 apart
Extend arms sideways to shoulder level
In rhythm
Flex elbow clasping fingers at nape of neck
Rotate elbows forward until they touch
Rotate elbows sideways
Unclasp fingers and extend arms sideways at shoulder level
Repeat

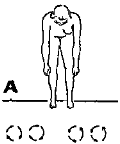
K



Lie on back with arms against the side of the body (use firm surface as floor with rug pad or blanket or f rm mattress without a pillow)
In rhythm
Raise arms to shoulder level (do not flex elbow)
Extend arms above head
Return arms to shoulder level
Lower arms to side
Repeat

Fig 35 7 Rehabilitation exercises for the patient following radical mastectomy

A



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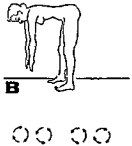

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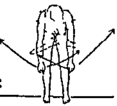

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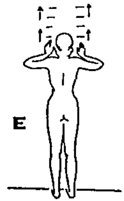

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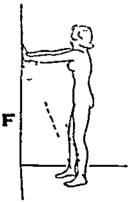


Stand w th feet 8 apart
Bend forward from the waist
Allow arms to hang toward the floor by gravity
Relax
In rhythm
Loosely swing both arms in a circle clockwise
Loosely swing both arms in a circle counter clockwise
Loosely swing each arm in opposite directions—outwards
Loosely swing each arm in opposite directions—inwards
Stand and allow arms to fall to s des

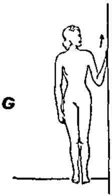
Stand with feet 8" apart
Bend forward from the waist allowing arms to hang toward the floor by gravity
Swing both arms together describing an arc from one shoulder to the other
Do not bend elbows
Stand; allow arms to fall to side

Stand with feet 8" apart
Bend forward from the waist allowing arms to hang toward the floor by gravity
In rhythm:
Swing both arms together describing an arc from over head to hip
Swing each arm in opposite directions describing an arc from over head to hip
Stand and allow arms to fall to side

Facing the wall and w th toes touching it stand against it with feet 8" apart
Bending the elbows place palms against the wall at shoulder level
Work the hands up the wall parallel to each oth r unt l *fully extended*
(Mark the wall each day at height reached to measure progress)
Work hands down to shoulder le el
Repeat

S and facing the wall at arm s length with feet 8" apart
Place hands against the wall at shoulder level parallel to each other
Slowly flex the elbow bending the trunk forward until forehead touches wall
Straighten elbows slowly unt l body is upright
Repeat
Note: Keep head trunk and legs in straight l ne

G

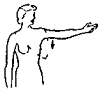


Stand at right angle to the wall with affected arm next to the wall
Place palm against the wall at shoulder level
Work the hand up the wall until fully extended
Work hand down to shoulder level
Repeat

H

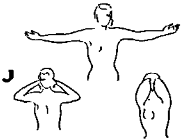
Stand with feet 8 apart
In rhythm
Extend arms sideways to shoulder level
Flex elbows touching fingers at nape of neck
Extend arms sideways to shoulder level
Flex elbows touching fingers at back of waist
Repeat

I



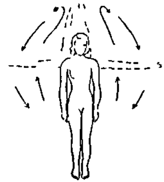
Stand with feet 8 apart
Extend affected arm sideways to shoulder level
In rhythm
Mov ng the arm forward flex elbow placing hand on opposite shoulder
Lower elbow against body
Raise elbow to shoulder level
Extend arm sideways to shoulder level
Repeat

J



Stand w th feet 8 apart
Extend arms sideways to shoulder level
In rhythm
Flex elbow clasping fingers at nape of neck
Rotate elbows forward until they touch
Rotate elbows sideways
Unclasp fingers and extend arms *sideways at shoulder level*
Repeat

K



Lie on back with arms against the side of the body (use firm surface as floor with rug pad or blanket or firm mattress without a pillow)
In rhythm
Raise arms to shoulder level (do not flex elbow)
Extend arms above head
Return arms to shoulder level
Lower arms to side
Repeat

Fig 35 7 Rehabilitation exercises for the patient following radical mastectomy

Care of the Wet Colostomy

Occasionally, the bladder and rectum along with other involved tissues may be resected and the ureters implanted in the remaining colon In this case the urinary and fecal discharges are expelled through the colostomy stoma Care of the skin is of great importance so that a bag can be applied as soon as possible Evacuation of these secretions is continuous and cannot be controlled by irrigation or diet Irrigation may start an ascending urinary infection A device successfully used for management of the wet colostomy is the Pierce bag which is applied with liquid adhesive making an airtight seal reinforced by plastic vinylite (Figure 35 5) Odors can also be controlled in this way The bag is emptied into the toilet at intervals but does not have to be removed for 2 to 3 days Chlorophyll employed in the solution used to wash the appliance or taken orally in tablets helps to control odors Charcoal also aids in the social acceptance of the patient by reducing flatus

Ureterostomies

Frequently, the ureters are implanted on the skin These ureterostomies have to be carefully managed to prevent retraction and maintain viability Ureteral catheters inserted at operation are kept clear of obstruction by *irrigation* If the ureterostomies are permanent they may be managed with the Singer cups (see Figure 35 6) These are applied with liquid adhesive and lead to the urinal strapped to the thigh

NURSING PROBLEMS OF PATIENTS WITH BREAST CANCER

The immediate postoperative care of the patient who has had a radical mastectomy presents several important nursing problems The pressure dressing around the chest makes postoperative lung aeration difficult Hemorrhage from the axilla and cyanosis of the hand are dangers for which the nurse should watch Naturally the pulse and blood pressure should be measured on the unaffected side The affected arm should be elevated and in a day or so the patient should begin to use it to comb her hair brush her teeth and take her bath Even before discharge an artificial breast can be used over the dressings during the healing period These wounds do well if cleaned frequently with spray and suction methods, using one of a variety of solutions

The rehabilitation of these patients involves the correction of the dropped shoulder and the limitation of arm movement by means of a plan for daily exercise Ten exercises designed for this purpose have been used successfully as a basis for group health teaching (see Figure 35 7) Of course, the limitation of function and degree of resumed activity depend on the "handedness" of the patient in relation to the region involved

SPECIAL NURSING PROCEDURES OF PATIENTS WITH CANCER OF THE HEAD AND NECK

The nursing care of patients with tumors of the head or neck presents special problems *in* the management of feeding breathing sensory disturbances and of wounds in contaminated areas of the mouth, nose, and throat

Oral hygiene is always the nurse's responsibility, but in this region it is of special importance since it contributes to the control of infection and pain If the mouth is ulcerated the power spray and suction technic can be *used very effectively*

Nasal feeding contributes to a clean mouth and throat both pre and postoperatively A *No 18 catheter slightly moistened* with a water soluble lubricant is held with the natural droop downward The catheter is directed through the larger nostril toward the lobe of the ear while the patient is instructed to swallow The end of the tube is encircled by an adhesive flange and pinned with a safety pin or by a rubber disk to prevent swallowing (see Figure 35 8) A test should be made after each insertion to be sure that the tube is not in the trachea If the patient coughs if air bubbles through the water when the flanged end is submerged or if inspection of the throat shows the tube to be directly in the mid line the tube should be withdrawn and reinserted The patient needing tube feeding for a period of time can be taught to insert his own tube and administer his own nourishment

To promote healing the wounds in the mouth and nose cavities should be kept clean

by frequent spray and suction Care should be taken not to touch the suture line Dobell s saline and peroxide are some of the solutions used Dressings saturated in activated zinc p roxide have been found to be particularly useful in preventing infections if packed along the suture line or affected area

The tracheostomy requires constant and meticulous care If the opening is temporary the nurse removes only the inner tube for cleaning The patient can be taught to suction

Fig 35-8 Nasal tube with disk

this tube and change it It is most important to do this often since the lumen is small and the secretions are tenacious and tend to crust The patient must cough at regular intervals holding a gauze apron over the stoma to catch the secretions When postoperative edema has subsided sufficiently to permit an adequate airway through the larynx then the inner tube may be removed corked and reinserted as ordered The cork should be tested for size on the lumen of the inner tracheostomy tube before inserting to prevent possible aspiration A black thread strung through the cork and taped to the skin is a special safety measure

If the stoma is permanent the mucosa is sutured to the skin which brings the cartilage ring of the trachea to the surface to keep the lumen open After a few days these patients may do very well without a tube However they should wear one at night to prevent occlusion of the stoma while sleeping

The ability of these patients to speak is temporarily interrupted A magic slate or some other device enables these patients to express themselves by writing

THE NURSING CARE OF PATIENTS RECEIVING RADIATION THERAPY

Special nursing care of the patient is related to protection of the skin or mucous membrane through which x rays are delivered and protection of the patient against systemic reaction or radiation sickness These subjects are discussed is detail in Chapter 29 The nurse plays a vital role in the maintenance of the necessary disciplines

Radium The nursing care of the patient should be planned so that the radium is applied and removed exactly when ordered (this is the doctor s responsibility) The patient s bedside should be labeled during this period and the patient should be kept in bed in the prescribed position lest the beam of radiation be diverted Contact with the patient should be reduced to a minimum

All radium should be counted before and after insertion and checked by the doctor If any is lost all activity should be halted until it is recovered by the radiologist or physicist Special precautions should be taken to prevent flushing down sinks hopper or toilets or discarding in waste cans or other refuse disposal units

Radioactive isotopes should be brought to the nursing unit and administered immediately

Nursing care of patients who are being treated with radioactive materials can be planned according to the following suggestions

1 Prepare as completely as possible for nursing care away from the bedside

2 Keep all sources of radiation away from all working areas and personnel

3 Store radioactive materials in the nursing unit no longer than is absolutely necessary

4 Always keep radioactive materials enclosed in carriers or containers that have been tested for adequate protection

5 Never discard anything suspected of con

taining radioactive material but report to proper authority for investigation

6 Handle all radioactive material with long handled instruments at arm s length

7 Wear gloves when handling isotopes

8 All personnel working with radioactive materials should wear monitors that are read monthly to ascertain safe minimum exposure

9 Periodic blood counts should be taken of exposed personnel

OTHER AGENTS

The quest for a lethal material specific to malignant tumor tissue has added a number of agents of palliative value These include chemicals such as nitrogen mustard antifolics urethane, etc hormones such as testosterone estrogens ACTH and cortisone, and toxins such as Coley s toxins The list is long and changing as the investigative processes go forward The nurse is part of this activity on the clinical level and makes a sensitive contribution to the findings In order to make the most effective contribution she should know the method of action, therapeutic dosages, method of administration, and toxicology of the drugs administered including expected and untoward reactions of the drug on the patient

Reporting End Results of Cancer Treatment

CHAPTER 36

Methods of Reporting End Results of Cancer Treatment

Eleanor J Macdonald

The choice of treatment for cancer has been determined by individual clinical experience with a rationale based on the state of current knowledge Results of these separate clinical experiences have been massed and reported in terms of survival with or without freedom of clinical symptoms of the disease The one objective criterion for measuring the effects of treatment against the disease cancer is increase in survival time resulting from the treatment used Despite the great volume of reporting the simplest questions still remain to be definitively answered Many of the accepted customs in cancer thinking have developed from the experience with cancer of the breast The large and increasing volume of recognized cases of this one site and the relatively early application of radical excision as the accepted treatment started a literature of descriptive and more recently of inductive analysis of the component parts of this problem Observation that metastases became clinically apparent in cancer of the breast with greatest frequency in the first and fourth years after treatment led to the arbitrary adoption of five years survival or freedom from disease as the criterion for evaluation of treatment or one year after the observed danger period in cancer of the breast This criterion was applied to all sites of cancer

Nathanson and Welch [10] in 1936 showed that the expectation of life for individuals with cancer of different sites paralleled the normal expectation of life after three years in some sites of cancer four in others and five in others and that in cancer of the breast there were fluctuations from normal after ten years By inference they showed that if a time limit were to be the determining factor in auditing results of treatment there should be different time limits for different sites This acute observation did not alter the custom of five year reporting although it did influence the periodic schedules recommended in many follow up programs

Intensive study is in progress toward the development of a more powerful technic for evaluating the effects of treatment in cancer It is historically interesting that one of the early efforts toward applying the experimental method to testing forms of treatment used in cancer in planned clinical trials designed to avoid the risks of bias inherent in unplanned studies is being made in the study of cancer of the breast It is realized now that established principles of good medical practice may be maintained while at the same time determination of the effect on the curability of cancer of the several methods of treatment currently used empirically may be evaluated through co operative clinical trials planned and carried out in collaboration with a statistician

This may well be the turning point in the attack on cancer In this period of transition while investigators search for answers acceptable by scientific standards to each of the inherent problems in assessing treatment and results for cancer the clinician in his daily practice will continue as he has done using the judgment i e has gained from experience The methods of reporting end results of treatment given here must be recognized as transitional pending the application of the modern method of clinical trials to the elucidation of

the effects of treatment in cancer

Efforts to evaluate the results of the care and treatment of cancer have led to a growing constructive literature devoted to the critical appraisal of current methods of reporting end results Among the best are the reviews by Hopkins [6] and Smithers [15] on breast cancer, by Tivey [17, 18, 19] on leukemia, by Berkson and Gage [3] Boag [4] and Lea [7], on other sites Hopkins has clearly stated the points at issue in the following

The basic problem we wish to solve is how best to estimate the probability of surviving through each of a succession of time intervals such as weeks months or years following our origin (onset of disease diagnosis beginning of therapy and so forth) A good method would (*a*) use all the information available from the data (*b*) provide early estimates i e considerably before the actual death of all the patients (*c*) make provision for competing risks of death from other causes (*d*) provide an estimate of the precision of our estimated mortality rate i e a standard error so that results of a series may be compared with other series and (*e*) be reasonably simple to understand and operate

In agreement with the other analysis of existing methods he described the three commonly used incorrect methods and their intrinsic defects as follows

1 The procedure of obtaining a survival rate by dividing one s patients alive at this moment by the total number of patients treated to date involves an obvious fallacy The risk of death (or of survival) being a function of the passage of time a composite figure which includes patients at risk for highly varying lengths of time cannot be interpreted If most of the patients had been treated quite recently the resultant survival rate would be high or if most were treated long ago the rate would be low [9]

2 To average the length of survival at death of those who have died up to this moment is similarly incorrect This again will give results that depend primarily on the length of the follow up period If the follow up is one year then the average survival of those who died can not possibly be more than one year With a five year follow up the average survival time of those who died will be about two and one half years and in any case cannot exceed five years Results of both these procedures are entirely artificial and tell us nothing about the risk of dying with cancer or the probability of surviving [9]

3 Various methods which seek to estimate the mean survival time or the total time survived by a group of patients are quite likely to be incorrect The distribution of survival times of well persons is very skewed [4 17, 18 19] and accumulating evidence supports the general expectation that survival times of most diseases whether of long or short duration present skewed distributions of approximately the log normal form For such a distribution the arithmetic mean is a quite atypical value and may be quite misleading The median or time at which 50 per cent of patients are dead is the preferred measure for summarizing the data as an average expectation

Four methods currently noted in the literature for handling the analysis of follow up data are the direct method the actuarial or life table method the Berkson Gage adaptation of the actuarial method using an exponential formula that takes into account the competing risks of death from other causes and the maximum likelihood method derived from Fisher developed further by Boag and Lea and applied by Tivey in a comprehensive survey of leukemia data

The first two methods are frequently encountered The third is becoming more familiar The maximum likelihood method is being used in several studies under way at this writing

Certain fundamental minimum requisites must be present before any method may be reasonably applied [8]

1 A clear definition of the limits of the anatomic site

2 Specific detail as to the geographic area from which the patients are drawn

3 A precise statement of the actual time interval involved

4 A statement of the total number of individuals diagnosed as having cancer of the anatomic site in question in the stated interval of time by year of entry into the series whether or not all were treated

5 A statement of the actual known status as to clinical presence or absence of disease at annual or more frequent regular time intervals of all individuals in the series so that rates may be computed showing freedom from disease and survival time

The statistics committee of the Memorial Cancer Center in New York City developed a form adopted in essence with some revisions by the joint committee of the American College of Surgeons the American College of Radiology the College of American

TABLE 36 1 —END RESULTS

This series consists of all the cases of all patients with (site of cancer) both early and advanced admitted to (name of hospital) in the stated year

Total Number of Patients Admitted

Indeterminate Group

Applied after treatment elsewhere no evidence of cancer on admission or thereafter
Consultation only no treatment requested
Patient refused proffered treatment or palliation
Dead of other causes without recurrence of cancer
Lost track of without recurrence of cancer
Total indeterminate results

Determinate Group

Total number minus those of indeterminate group

Failure

Dead as a result of cancer
Operative death
Dead of other causes cancer present
Living with recurrent cancer
Dead of other causes unknown whether cancer present
Lost track of with cancer
Lost track of possibility of recurrent cancer unknown
Total failures in treatment

Successful Results

Free from cancer

Net End Results

Successful results divided by determinate group

All cases reported as cured have been pathologically proved to have had cancer Lack of pathologic proof does not exclude failures

Pathologists the American Cancer Society and the National Cancer Institue [1] It has a listing enabling concise accounting for every individual with cancer of a given site known to the hospital state registry or physician as the case might be in the time interval under consideration It was planned as a five year reporting form but is more efficiently used when each year s admissions are given separately together with the status at annual intervals to the moment of reporting The table headings are listed and are self explanatory

If criteria for clinical staging were stated generally accepted and consistently reported one series could be compared with another and valid conclusions could be drawn about the relative influence of the several factors that determine prognosis Committees composed of membership from countries all over the world are presently at work on the problem of staging of breast cancer as the Heymann committee worked out the staging of the cervix uteri The frequently expressed wish that this be done portends well for its universal adoption once it is agreed upon

The four methods referred to above will be discussed in the stated order

1 The direct method of calculating survival rates with or without clinical evidence of cancer is the usual one encountered and has the advantage of being readily understood and easily applied It lists the number of patients seen the number traced and the number alive at each time interval The calculation of these rates at yearly rather than at five year intervals was recommended by the World Health Organization subcommittee on the registration of cases of cancer and their statistical presentation and reported by Clem

mesen in 1951 [5] On series that are small the descending survival curve is not always consistent, but on large series the method approximates the results obtained by more elaborate mathematical approaches The important requisite to the use of this method correctly is to have adequate follow up so that the proportion of untraced patients is small If the untraced are omitted when rates are calculated, it is assumed that their mortality rate is the same as the rate of the traced cases

2 The actuarial method is generally used in Great Britain where it was recommended by Dr Percy Stocks Chief Statistician (Medical) General Register Office [16] From a life table the total months are calculated that would be lived in a period of observation by a group of individuals in the general population with the same age sex distribution as the group of patients under consideration This gives the mean number of months of expected life during the stated period by each group The mean number of months actually lived is then calculated for each time interval It is expressed as a percentage of the normal expected for that group making allowances for cases followed for less than the stated intervals of time

An excellent demonstration of the actuarial as compared with the direct method of calculating survival rates is given by Berkson [2] Berkson demonstrates that rates calculated by the direct method in a well followed series could be almost the same as those determined by the actuarial method although such is not always the case The difference arises because of the size of the number of untraced patients If data consisted of a single group all members of which were followed continuously for the same period both methods would give identical answers For practical knowledge of methodology calculating survival rates in the actuarial sense Berkson s chapter is recommended [2]

3 In the Berkson Gage [3] adaptation of the actuarial method observation that survival curves followed a relatively uniform pattern led them to work out the formula of that curve This is the exponential formula enabling estimation of the effectiveness of cancer therapy from the study of experience based on a few years rather than on the time to death of all patients in the series

$$l_t = cl + (1.00 - c)\ l\ e^{-\beta t}$$

l is P (survival in total population) determined by the actuarial method

l_0 is P (survival in a population subject to death only from diseases other than cancer), obtained from a suitable life table

c is fraction of total population "cured" In essence this means the fraction still survivin after all the deaths due to cancer may be assumed to have occurred

Beta is the instantaneous cancer death rate assumed to be constant

This method takes fully into account the competing risks of death from other causes It involves estimation of only two parameters β and c This estimation is made rather easily by a graphic method

Berkson and Gage add a further feature which makes their method attractive for clinical presentation They summarize the constants obtained from their analysis in the form of expectation of life of the cancer patient as a per cent of normal expectation of a healthy person of same age and sex [6]

4 The maximum likelihood method is an efficient way of using all the information available in the data Survival curves generally follow a skewed distribution This is because in many forms of cancer the majority of patients die shortly after onset well before their average expectation of survival time and that others live for longer periods of time than expected Boag observing this skewed distribution demonstrated that the logarithms of survival times are normally distributed In order to transform these skewed survival curves into a normal distribution, readily analyzed by conventional statistical methods the frequencies are plotted against the logarithm of survival time and are called the log normal distribution

This log normal distribution is completely specified by its mean mu and its standard deviation sigma The proportion cured is denoted by c The fundamental problem is concerned with the simultaneous estimation of these three quantities Boag has worked out rather elaborate formulas for estimating mu sigma and c from the information obtained early in the clinical trial rather than at the time all patients have died to find out the proportion of patients who died free of cancer Lea evolved a simple method of making the

same basic estimates and the classic papers of Tivey demonstrate the method in use in arriving at the prognosis for survival in leukemia

The solution of the basic problem as set forth by Hopkins can be approximated by any of the four methods described There is a possibility that great differences are occurring in certain anatomic regions in different institutions

To make all results available by a uniform method of reporting and to follow this by an analysis of the underlying causes for differences, would reward with a directive toward success the sincere and constant effort of every physician treating individuals with cancer to improve the prognosis for his patients

A sound experimental design for each investigation is prerequisite to the definitive evaluation of the results of treatment

CHAPTER 37

Specific Methods of Calculating Survival Rates of Patients with Cancer

Joseph Berkson
and
Robert P Gage

One of the chief dependable indexes for gauging the effectiveness of the treatment of malignant tumors is the observation of the length of life of the treated patients This has long been recognized by physicians and surgeons and the presentation of 5 year cures is an old and firmly established item in the medical literature of treated cancer Unhappily, the quality of the calculations as reported is frequently not above criticism, numerical data essential for meaningful interpretation may be lacking and there even may be evidence of erroneous calculation of the rates themselves This is not too surprising since the valid calculation of these rates is considering the type of data available to the physician often a matter of considerable statistical complexity though once the essential principles are grasped it is not difficult to accomplish At the Mayo Clinic a systematic program has been in operation for many years with the objective of ascertaining the survival curves for all patients with malignant tumors treated surgically We are presenting an outline of the methods followed by the Section of Biometry and Medical Statistics in the calculation of these rates and for the summary presentation of results

We may start by reference to the 5 year survival rate This is what in surgical circles is sometimes called the 5 year cures * In essence what is wanted is simple enough Beginning with a given number of patients what per cent will be alive in 5 years? The group with which we begin may be variously defined for instance it may be the group of patients who have been diagnosed to have the malignant lesion or it may be the ones who have undergone operation or it may be only those who have survived operation The rates for these different groups obviously will be different but so long as the basic group is defined unequivocally the meaning of the rate is clear it gives the probability for the defined group of surviving 5 or more years If we know the survival rate for the group of patients who have survived operation we can calculate the rate referring to the total group for whom diagnosis was made as will be explained later if we know also the operability rate and the hospital death rate However chiefly in this article we are concerned with the calculation of the rate that refers to the group of patients who have survived operation

We shall give two methods for calculating this rate (1) the *ad hoc* or direct method (2) the actuarial method

THE DIRECT OR AD HOC METHOD

We are generally interested not only in the 5 year rate but also perhaps in the 10 year rate the 15 year rate and so forth In each instance we mean the probability in a group of patients who have survived the operation

* The phrase cure rate should not be used for this estimate There is no biologically reliable method of determining for a particular individual whether he has been cured that is completely freed of a cancerous process Some attempts have been made to estimate the proportion cured by statistical methods [1 -] that go beyond what is presented here

of living beyond the specified number of years If we were to start with say 500 patients who have just left the hospital alive and to observe each member of this group until death and to enumerate the individuals who survive 5 years those who survive 10 years and 15 years then the ratio of these respective numbers to the original 500 gives successively an estimate of the 5 year 10 year, and 15 year survival rate* after leaving the hospital This is the quite simple idea But in dealing with the usual sort of data available for patients with malignant tumors we do not literally begin with such a group and follow them all continuously and uniformly until death before calculating survival rates and with such data as we do have certain relevant facts must be attended to in order to calculate the rates properly

The group considered will generally include individuals who have undergone operation at different times spreading over many years so that the different individuals will have been observed for different lengths of time At the time of investigation some of the group will have died and the time of death will be known some will be known to be dead but the time of death will be unknown others will be known to be alive at the time of investigation and some will have been lost track of and it will not be known whether they are alive or dead Such a body of heterogeneous data is to be assembled for the calculation of say the 5 year 10 year and 15 year survival rates after leaving the hospital

We shall begin with the 5 year rate and we shall assume that the date of investigation is as of January 1 1953 We have say in all 500 patients in our series who have undergone operation and survived the operation Since not all the patients have been followed until the time of death for some are still living it is not possible to use the entire group of 500 Some of them have undergone operation in the last 5 years (from January 1 1948 through December 31 1952) and among these latter are living patients who may or may not be destined to survive 5 years We must begin with a group exposed to the risk of surviving 5 years which means simply that we begin by excluding the patients who have undergone operation more recently than 5 years ago Suppose these number 100 then we shall include the rest of the group—400 patients who underwent operation prior to January 1 1948 Of these 400 patients we wish to know how many survived 5 years after their leaving the hospital For those dead with time of death known we shall know whether or not they have survived for 5 years equally clearly those alive at the time of investigation will have lived for at least the 5 year period and some patients alive when last heard of but then lost will have passed the 5 year mark But there will be a certain number say 10 who are known to be dead but the time of whose death is unknown and a certain number say 30 who had been living at last report but who had been lost track of less than 5 years after the time of their leaving the hospital As regards the latter two groups we do not know whether they did or did not live for the 5 year period and the 40 patients together constitute a group we call untraced

Actually therefore because of these 40 patients we do not know the number of individuals out of the original 400 who survived 5 years and in a literal sense we cannot calculate the desired rate directly and simply In order to make an estimate, it is necessary to make an assumption regarding the untraced group We can (1) assume that they all died in less than the 5 year period and in that case we shall divide the number definitely known to have lived more than 5 years by the total 400 or (2) we may assume that they all lived beyond the 5 years or (3) we may leave the untraced group out of the calculations and divide the number known to have lived for 5 years by the total number exposed minus the number untraced In the present case these number $400-40=360$ * This last procedure is mathematically equivalent to making the assumption that the

* The expression survival rate is used in this article as synonymous with probability of surviving Similarly in what follows the term death rate is used loosely as synonymous with probability of dying although as usually defined there is a technical difference between the death rate in an interval and the probability of dying in the interval.

* There are still other possibilities of course we can use some theory regarding the probabilities of *becoming untraced* and elaborate an estimate consistent with the theory adopted This presentation does not deal with such development

survival rate for the "untraced group what ever the rate is is equal to that for the traced group It is the least arbitrary of the three assumptions and in our own calculations it is this method that is used, that is, we omit the untraced group in making the calculation of the rate Obviously there is a hazard in making *any* assumption, and the final calculated rate is subject to whatever error is implicit in the assumption made regarding the untraced group Clearly it is desirable to reduce this uncertainty by reducing the number of 'untraced patients It is for this reason that in our studies we have made exhaustive efforts to trace all our patients and we have been successful generally for our larger series in tracing more than 99 per cent for the requisite numbers of years

Now for the calculation of the 10 year rate Previously we dealt with the group of 400 patients who had undergone operation prior to January 1 1948 The 10 year rate is not determined by merely dividing into this total or even into the previously determined traced total the number who survived 10 years We must first obtain the number exposed to risk of surviving for 10 years Of the group of patients who underwent operation prior to January 1 1948 previously used the patients who underwent operation in the period January 1 1943 through December 31 1947 though they were exposed for 5 years have not been exposed for 10 years This subgroup must first be excluded and we take up therefore the group who underwent operation prior to January 1 1943 It might appear superfluous to stress this point but surprising as it may seem one of the errors most frequently encountered is just this failure to select the proper exposed to risk group for each particular rate to be calculated And it is not so difficult to slip into this error An author begins by considering his entire experience of patients who have undergone operation to date He reports certain general statistical facts about this entire experience such as the hospital mortality rate the age and sex distribution pathology and so forth He comes to the point of calculating survivals and carefully counts the number recorded as having lived past the 5 year 10 year and 15 year mark It seems natural to express these percentagewise, by dividing the several numbers of survivals by the total number in the group he has been dealing with Instead of course he should determine an appropriate new total for each survival calculation The effect of dividing by the grand total is to underestimate sometimes grossly the true survival rates With the proper total group selected the calculation of the 10 year rate follows simply, in the same manner as for the 5 year rate, and so for the 15 year rate or other interval rate to be calculated In presenting the results it is essential that for each calculated rate the three essential numbers involved be given the number in the total group, the number in the traced group and the number that have survived Table 37 1 is an

TABLE 37 1 —EXAMPLE OF TABLE FOR PRESENTATION OF SURVIVAL RATES CALCULATED BY THE DIRECT METHOD

1	*2*	*3*	*4*	*5*
	Patients		*Lived beyond indicated period*	
Period years	*Total*	*Traced*	*Number*	*Survival rate per cent**
5	379	376	286	76 1
10	286	283	165	58 3
15	164	160	75	46 9

Per cent of traced patients Inquiry as of January 1 1953 The 5 year group comprises patients who underwent operation 5 or more years prior to the time of inquiry that is 1947 or earlier the 10 year group includes those patients who underwent operation in 1942 or earlier and so forth Hospital mortality is excluded in the calculation of the survival rates

example of how this may be done and the information given in the footnote of that table is essential

If the standard error of the survival rate computed by the direct method is wanted the following formula may be used

$$\sigma(p) = \sqrt{\frac{pq}{N}}$$

where $\sigma(p)$ is the required standard error p is the survival rate calculated σ $p=1-p$ is its complement the death rate and N is the number traced on which the calculated rate is based

It will possibly be useful to append some advice regarding the clerical management of

the data to obtain the needed figures In this Section since we have the necessary machinery we generally utilize punch cards sorted mechanically However, this is not necessary Frequently when the numbers involved are moderate we do not use *punch* cards but we always use *cards* It is possible to get the several requisite figures by listing the appropriate categories on a sheet entering a check for each case in the appropriate category and counting the check marks For a large number of cases this becomes very confusing and if the tables do not balance, location of the source of error is practically impossible without repetition of the entire work Instead we suggest the following method For each case a card is made (3×5 inch card or any other paper unit) In addition to identification and such other information as may be required for the general analysis the following data are entered for purposes of calculating the survival rate (1) date of operation (2) whether living at last report [*l*] or dead at last report [*d*] (3) date of last report (4) interval from operation to last report in completed years Example

Date of operation February 11 1943
Last report *l* Interval 6
Date January 16 1950

Note that the interval is entered as completed years 6 although the actual interval is 6 years 11 months 5 days the entered figure 6 is a code meaning 6 years or more less than 7 years

With a card bearing these three data completed for each case proceed as outlined in Figure 37 1

1 Examine the *date of operation* exclude all cards indicating that the operation was performed more recently than 5 years prior to the date of investigation In the situation being considered this means any case in which operation was performed in 1948 or later

2 Count the number of cards in the remaining group that is those operated on in 1947 or earlier this is the number of patients who are eligible for the 5 year calculation to be entered in Column 2 of Table 37 1

3 Now subdivide the cards of the previous group 2 into two groups on the item *interval* (A) those marked 5 or more (B) those marked 4 or less Count those in group (A) this is the number of patients who lived 5 or more years after operation, to be entered in Column 4

4 Take up the cards in group (B) which are the cases with interval 4 years or less and separate them into two groups on the item *last report* , (a) dead (b) living By counting the cards marked dead (a) and adding this number to the number recorded in Column 4 of Table 37 1 (lived more than 5 years) we obtain the number traced 5 or more years, to be entered in Column 3

5 We have now obtained all the data necessary for the calculation of the survival rate

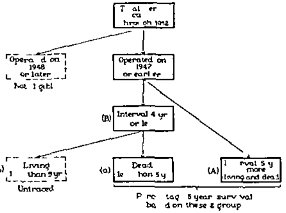


Fig 37 1 Diagram of steps taken in calculation of the 5 year survival rate by the direct method

this rate being entered in Column 5

6 Finally by counting the cards in group (b) marked *last report* living which are the untraced cases and adding this to the number of traced cases appearing in Column 3 we obtain a check of the total cases counted earlier appearing in Column 1

CALCULATION BY THE ACTUARIAL METHOD

The direct method just outlined for calculating the survival rate is a reasonably satisfactory one and in most instances in which a calculation is to be made as part of a study in which the presentation of the survival rate is not the main consideration it is the method that we advise physicians and surgeons to use in publication intended for medical readers Technically however it is not the

survival rate for the untraced group what ever the rate is is equal to that for the traced group *It is the least arbitrary* of the three assumptions and in our own calculations it is this method that is used, that is, we omit the untraced group in making the calculation of the rate Obviously there is a hazard in making *any* assumption and the final calculated rate is subject to whatever error is implicit in the assumption made regarding the untraced group Clearly it is desirable to reduce this uncertainty by reducing the number of 'un traced patients It is for this reason that in our studies we have made exhaustive efforts *to trace all our patients* and we have been successful generally for our larger series in tracing more than 99 per cent for the requisite numbers of years

Now for the calculation of the 10 year rate Previously we dealt with the group of 400 patients who had undergone operation prior to January 1 1948 The 10 year rate is not determined by merely dividing into this total or even into the previously determined traced total the number who survived 10 years We must first obtain the number exposed to risk of surviving for 10 years Of the group of patients who underwent operation prior to January 1 1948 previously used the patients who underwent operation in the period January 1 1943 through December 31 1947 though they were exposed for 5 years have *not been exposed for 10 years* This subgroup must first be excluded and we take up therefore the group who underwent operation prior to January 1 1943 It might appear superfluous to stress this point but surprising as it may seem one of the errors most frequently encountered is just this failure to select the proper exposed to risk group for each particular rate to be calculated And it is not so difficult to slip into this error An author begins by considering his entire experience of patients who have undergone operation to date He reports certain general statistical facts about this entire experience such as the hospital mortality rate the age and sex distribution pathology and so forth He comes to the point of calculating survivals and carefully counts the number recorded as having lived past the 5 year 10 year and 15 *year mark* It seems natural to express these percentagewise by dividing the several numbers of survivals by the total number in the group he has been dealing with Instead of course he should determine *an appropriate* new total for each survival calculation The effect of dividing by the grand total *is to* underestimate sometimes grossly *the true* survival rates With the proper total group selected the calculation of the 10 year rate follows simply, in the same manner as for the 5 year rate and so for the 15 year rate or other interval rate to be calculated In presenting the results it is essential that for each calculated rate, the three essential numbers involved be given the number in the total group the number *in the traced group and the* number that have survived Table 37 1 is an example of how this may be done and the information given in the footnote of that table is essential

TABLE 37 1 —Example of Table for Presentation of Survival Rates Calculated by the Direct Method

1	*2*	*3*	*4*	*5*
	Patients		*Lived beyond indicated period*	
Period years	*Total*	*Traced*	*Number*	*Survival rate per cent**
5	379	376	286	76 1
10	286	283	165	58 3
15	164	160	75	46 9

Per cent of traced patients Inquiry as of January 1 1953 The 5 year group comprises patients who underwent operation 5 or more years prior to the time of inquiry that is 1947 or earlier the 10 year group includes those patient who und r went operation in 1942 or earlier and so forth Hospital mortality is excluded in the calculation of the survival rates

If the standard error of the survival rate computed by the direct method, is wanted the following formula may be used

$$\sigma(p) = \sqrt{\frac{pq}{N}}$$

where $\sigma(p)$ is the required standard error, p is the survival rate calculated σ $p=1-p$ is its complement the death rate and N is the number traced on which the calculated rate is based

It will possibly be useful to append some advice regarding the clerical management of

the data to obtain the needed figures In this Section since we have the necessary machinery we generally utilize punch cards sorted mechanically However this is not necessary Frequently when the numbers involved are moderate we do not use *punch* cards but we always use *cards* It is possible to get the several requisite figures by listing the appropriate categories on a sheet entering a check for each case in the appropriate category and counting the check marks For a large number of cases this becomes very confusing and if the tables do not balance location of the source of error is practically impossible without repetition of the entire work Instead we suggest the following method For each case a card is made (3×5 inch card or any other paper unit) In addition to identification and such other information as may be required for the general analysis the following data are entered for purposes of calculating the survival rate (1) date of operation (2) whether living at last report [*l*] or dead at last report [*d*] (3) date of last report (4) interval from operation to last report in completed years Example

Date of operation February 11 1943
Last report *l* Interval 6
Date January 16 1950

Note that the interval is entered as completed years 6 although the actual interval is 6 years 11 months 5 days the entered figure 6 is a code meaning 6 years or more less than 7 years

With a card bearing these three data completed for each case proceed as outlined in Figure 37 1

1 Examine the *date of operation* exclude all cards indicating that the operation was performed more recently than 5 years prior to the date of investigation In the situation being considered this means any case in which operation was performed in 1948 or later

2 Count the number of cards in the remaining group that is those operated on in 1947 or earlier this is the number of patients who are eligible for the 5 year calculation to be entered in Column 2 of Table 37 1

3 Now subdivide the cards of the previous group 2 into two groups on the item '*interval*' (A) those marked 5 or more (B) those marked 4 or less Count those in group (A), this is the number of patients who lived 5 or more years after operation to be entered in Column 4

4 Take up the cards in group (B) which are the cases with interval 4 years or less and separate them into two groups on the item *last report* (a) dead (b) living By counting the cards marked dead (a) and adding this number to the number recorded in Column 4 of Table 37 1 (lived more than 5 years) we obtain the number traced 5 or more years to be entered in Column 3

5 We have now obtained all the data necessary for the calculation of the survival rate,

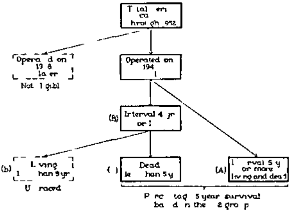


Fig 37 1 Diagram of steps taken in calculation of the 5 year survival rate by the direct method

this rate being entered in Column 5

6 Finally by counting the cards in group (b) marked *last report* living which are the untraced cases and adding this to the number of traced cases appearing in Column 3 we obtain a check of the total cases counted earlier appearing in Column 1

CALCULATION BY THE ACTUARIAL METHOD

The direct method just outlined for calculating the survival rate is a reasonably satisfactory one and in most instances in which a calculation is to be made as part of a study in which the presentation of the survival rate is not the main consideration it is the method that we advise physicians and surgeons to use in publication intended for medical readers Technically however it is not the

best method available For a large number of cases the direct method and the actuarial method presently to be described will give practically the same answer but for a small number of cases the direct method will give an estimate that is subject to a larger standard error than that given by the actuarial method It may even give inconsistent results such as the calculated 10 year survival rate appearing higher than the 5 year rate! In addition to the advantage of giving a statistically better estimate the actuarial method is for some situations arithmetically easier If what is to be calculated is only the 5 year rate or perhaps the 5 year 10 year and 15 year rates, the direct method is probably easier than the actuarial method but when what one wishes is the *survival curve*—that is the successive rates for 1 2 3 years and so forth consecutively then the successive calculation of each yearly rate by the direct method becomes very laborious and the actuarial method is distinctly to be preferred Therefore in technical calculations from the Section of Statistics or where the survival curve is a central part of the study reported we advise the use of the actuarial method

To present the actuarial method we begin by considering the complement of the survival rate or probability of surviving namely the probability of dying that is the death rate

If beginning with an original group of say *100 patients who have left the hospital* alive 25 die in the course of the first year following we say that the estimate of the probability of dying in the year following the origin is 0 25 symbolized q_0 This would leave 75 alive at the beginning of the second year and if out of these 30 per cent died during the ensuing year we say that the probability having survived to the end of the first year of dying in the next year (1 2) is 0 30 symbolized q_1 Similarly the probability having survived to the end of the second year of dying in the next year (2 3) is q_2 say 0 24 and in the same way the probabilities of dying within the other successive years are symbolized q_3 q_4 q and so forth If we wish to have say the 3 year survival rate we may begin with a hypothetical 1 000 multiply by q_0 and obtain 250 as the number having died in the first year Subtracting this from 1 000 leaves 750 alive at the end of the first year Multiplying 750 by q_1 gives 225 as having died in the second year, and subtracting these from 750 gives 525 left at the end of the second year Multiplying 525 by q gives 126 as having died in the third year and subtracting from 525 gives 399 left at the end of the third year This last number, in ratio to the original 1,000 gives 0 399 or 39 9 per cent as the 3 year survival rate after leaving the hospital If the data consisted actually of an original group continuously and uniformly followed as just outlined we could have noted that 399 patients had survived to the end of the third year and by division obtained the 3 year survival rate directly without the intermediate successive multiplication by the qs and subtractions The two methods would have given identical answers and there would be no need to speak of two methods But as we have noted actual data do not refer to a single group all members of which have been continuously followed and for the same period of time from this fact arises a difference in the results according as the survival rate is calculated by the direct method outlined in the previous section or by the actuarial method

The actuarial method consists as was just explained in the successive application to a hypothetical original number, of the probabilities of dying q_0 q_1 q q_3 and so forth *we need to determine from* our data what are the values of these probabilities We can do this conveniently by assembling the data in a methodical way This is shown in Table 37 2 which we shall follow

The first column designates the interval in years from the origin which here is the time of leaving the hospital Columns 2 and 3 give the number of persons for whom the period between leaving the hospital and the last report corresponds to the designated interval Column 2 giving the number dead and Column 3 the number living Column 4 gives the number of persons who were observed living at the beginning of the interval The rest of the columns are completed by calculation from the numbers in Columns 2 3 and 4

We assume that a card has been made out for each case and that on it is (1) the last report (living *l*, or dead *d*) and (2) the

TABLE 37 2 —CALCULATION OF SURVIVAL RATES BY THE ACTUARIAL METHOD

1	2	3	4	5	6	7
Interval following hospital dismissal years	*Last report*		*Total persons living at beginning of interval*	*Persons adjusted*	*Probability of dying in interval*	*Survival rate per cent*
	Dead	*Living*				
0 1	184	—	728	728 0	0 2527	100
1 2	156	13	544	537 5	0 2902	74 7
2 3	89	8	375	371 0	0 2399	53 0
3 4	36	4	278	276 0	0 1304	40 3
4 5	31	4	238	236 0	0 1314	35 1
5 6	16	9	203	198 5	0 0806	30 5
6 7	8	3	178	176 5	0 0453	28 0
7 8	7	13	167	160 5	0 0436	26 7
8 9	6	5	147	144 5	0 0415	25 6
9 10	7	8	136	132 0	0 0530	24 5
10+	52	69	121	—	—	23 2

interval in completed years from operation to last report These two data are all that will be needed

A Divide the total group of cards into two subgroups (1) dead at last report (d) (2) living at last report (l)

B Sort each of the two subgroups in order of length of *interval* 0 1 2 and so forth

C Completion of Column 2 Take up the group A (1) dead last report Count the cards marked 0 in the *interval* (all cases in which last report is less than a complete year from origin should have been marked 0) enter the number (184) in Column 2 opposite the interval 0 1 Count the cards marked 1 in the *interval* enter the number (156) opposite interval 1 2 count the number of cards marked 2 and enter this number (89) opposite 2 3 and so forth for completion of column 2

D Completion of Column 3 This is done exactly as for Column 2 except that the group of cards A (2) living last report is used

E Completion of Column 4 This column gives the number of persons living at the beginning of the interval The required numbers can most easily be obtained by cumulative summation of Columns 2 and 3 beginning at the bottom We add 52+69=121 121+7+8=136 136+6+5=147 and so forth until we have filled all the intervals including the first for which the number is 728 The cumulation gives the required numbers because the number living at the beginning of any interval must be the sum of all those reported living or dead in that interval or later One can also think of the experience as having begun with 728 persons 184 died in the interval 0 1 year after operation leaving 544 living at the beginning of the 1 2 interval Of these 544 156 persons died and 13 left the experience living in the 1 2 year interval leaving 375 living at the beginning of the 2 3 year interval after operation and so forth

F Completion of Column 5 At the beginning of the interval 0 1 there were 728 persons living and of these 184 died in the interval so the probability of death in this interval is estimated as $q_0=\frac{184}{728}=0\ 2527$ At the beginning of the interval 1 2 years there were 544 persons living of whom 156 were observed to have died in the interval However we cannot correctly estimate q_1 as $q_1=\frac{156}{544}$ because an adjustment has to be made in the denominator 544 for the 13 persons last observed living in the interval This adjustment is made by subtracting from the persons observed living at the beginning of the interval given in Column 4 (544) half the number given in Column 3 (6 5) to give the net number of persons adjusted entered in Column 5

The theoretical basis for this correction has been elaborated by Dr Lila Elveback in an unpublished manuscript, following a development by one of the present writers (Berkson) that can be briefly outlined as follows The maximum likelihood estimate for the probability of death in the interval is given by

$$q=\frac{D}{N-\sum_{i=1}^{L}\frac{(1-t_i)}{1-q\,t_i}}$$

where D is the number of deaths observed in the interval, N the number of individuals observed living at the beginning of the interval t_i the time last observed living of the ith individual among L last observed living in the interval the summation being taken over the L individuals If as an approximation t_i is taken as ½ for all L individuals, the estimate becomes $q=\dfrac{D}{N-\dfrac{L}{2-q}}$ and with small q this can be further approximated as $q=\dfrac{D}{N-\dfrac{L}{2}}$ which is the formula used here It should be noted that this formulation is different from the life year formula used by actuaries [7]

G Completion of Column 6 We are now able to calculate the probability of dying in the interval There were 184 deaths in the interval 0 1 (Column 2) and 728 persons adjusted (Column 5) therefore $q_0=184/728=0\,2527$ entered in Column 6 similarly $q_1=156/537\,5=0\,2902$ In this manner the probabilities of death in the successive intervals are calculated by dividing the number in Column 2 by that in Column 5 for completion of Column 6 for all the intervals

H Completion of Column 7 We now begin in Column 7 with a hypothetical 100 persons * Of these a fraction 0 2527 or 25 27 individuals will die in the interval leaving 74 73 living at the beginning of interval 1 2 Of the 74 73 the fraction 29 02 or 21 69 individuals will die during the interval 1 2 leaving 53 04, out of the original 100, living at the beginning of the 2 3 interval this being the 2 year survival rate In this way by successive application of the determined values of q that have been entered in Column 6 the survival rates for the successive years are determined and entered in Column 7

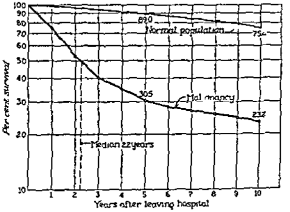


Fig 37 2 Percentage of patients who after having undergone operation for cancer survived for various periods after leaving the hospital These percentages are compared with the similar percentages of survival of normal persons of the same beginning age as the cancer patients

These survival rates which give the probability of surviving for specified numbers of years after leaving the hospital may be represented as a survival curve together with a survival curve representing a group of the same beginning age as the cancer group the rates for which are obtainable from rates published by the National Office of Vital Statistics as illustrated in Figure 37 2

If a standard error is wanted for the survival rate when it is calculated by the actuarial method the following formula (due to Greenwood) may be used

$$\sigma(p)=p\sqrt{\frac{q_0}{n_0p_0}+\frac{q_1}{n_1p_1}+\frac{q}{n\,p}+\cdots}$$

where $\sigma(p)$ is the required standard error p is the survival rate calculated n_0 is the number living at the beginning of the 0–1 year interval after operation q_0 and $p_0=1-q_0$ are respectively the death rate and the proportion surviving among the n_0 n_1 q_1, p_1 are

* One hundred because we are to express the rate in per cent we could begin with 1 000 and express the rates as per thousand or similarly per 100 000 All these are different expressions for the same rate The number we start with is symbolized l and the numbers surviving out of this original number at the successive years are symbolized l_1 l_2 l_3 and so forth

the similar quantities for the interval 1–2 years after operation and so forth The sum under the square root is continued for the intervals up to the 5 10 or whatever year p the survival rate represents

SOME SPECIAL QUESTIONS

Survival Rate for Total Group Diagnosed

We frequently encounter the query What is the percentage [of 5 year survivors] for the entire group of patients [with the cancer in question] as they came to the physician rather than for the group of patients who underwent operation? As far as basic principle is concerned the survival rate for the total group diagnosed can be obtained in exactly the same way as was outlined for the group who underwent operation merely by beginning with the total group of patients diagnosed instead of the surgical group In practice this is not the case because of the marked difference in the constitution of the groups If we are asked to designate the patients who underwent operation for say gastric carcinoma there is little ambiguity we have at least a surgical diagnosis and very frequently a specimen diagnosis But the relevant definition of the total group with the diagnosis including those who did not undergo operation is not so clear There are patients who had already undergone operation previously others who had a diagnosis who do not undergo operation but will undergo operation later those whose diagnosis is not absolutely unequivocal say as between gastric ulcer and a malignant lesion and of course we must always assume that there are some cases that have not been correctly diagnosed There is also quite a different problem as respects follow up tracing for this group

It does not seem wise to mix in the same calculation a group so heterogeneous in respect to definition and a well defined group Actually among the nonoperative cases the only well defined diagnostic group is the one in which the diagnosis reads to the effect "gastric cancer inoperable Now for this specific group the 5 year survival rate is presumably zero It may be very worth while as a special investigation to trace a representative number of such patients in order to check the validity of this assumption but in general calculations it seems better to assume that their survival rate is practically zero and to estimate the 5 year rate by compounding this probability weighted by the determined surgical rate rather than to begin literally with a total diagnosed group and attempt to trace them The calculation of the 5 year rate for the entire diagnostic group is then made as follows

Assume we start with a hypothetical group of 100 patients with the diagnosis in question By an independent statistical analysis of the experience with patients having this diagnosis determine the surgical rate that is the percentage of patients with the diagnosis who undergo operation Suppose this is 85 per cent Similarly by a review of patients who undergo operation we determine the hospital mortality rate' that is the percentage of patients undergoing operation who die following operation before leaving the hospital Say this is 5 per cent, then 95 per cent is the hospital survival rate The 5 year survival rate for persons operated on is calculated in the manner described in detail previously say it is 60 per cent Then the 5 year rate for the beginning group is estimated as $p_5 = 0\,85 \times 0\,95 \times 0\,60 = 48\,5$ per cent

Adjustment of Rate for Age of Patients

In the field of vital statistics survivorship curves are calculated as from birth for successive years after birth that is age and the successive values of q the probabilities of dying in the intervals specified are age specific probabilities [5] Whereas in the present problem we calculate the specific death rate for say the third year following the patients leaving the hospital in the general life table we calculate the specific death rate for the third year of life In the general life table *age* is the all important factor In the 5 year rate for cancer we consider years after operation (operative age so to speak) but the calendar age has not been used This is because the primary consideration is the time of operation not the time of birth that affects the mortality rate

But it is desirable if possible also to take into account in some way the age of the patients for it might be argued that *it is in*correct to compare the survival rate of one group of patients who are young with that of

TABLE 37 3 —CARCINOMA OF THE STOMACH CASES OF RESECTION 5 YEAR SURVIVALS ACCORDING TO AGE

	Patients		*Lived 5 or more years after leaving hospital*		
Age years	*Total*	*Traced*	*Number*	*Survival rate per cent**	*Survival rate adjusted for normal death rate*
Less than 40	206	203	61	30 0	30 9
40 49	672	666	203	30 5	32 2
50 59	1 118	1 110	342	30 8	34 3
60 69	976	971	300	30 9	39 1
70+	240	239	70	29 3	50 2
Total	3 212	3 189	976	30 6	34 4

Per cent of traced patients Inquiry as of January 1 19 3 The 5 year group comprises patients who underwent operation 5 or more years prior to the time of inquiry that is 1947 or earlier the 10 year group includes those patients who underwent operation in 1942 or earlier and so forth Hospital mortality is excluded in the calculation of the survival rates

Average Duration of Life

The *survival rate* expressed as the per cent living after a specified period is less familiar as a measure of length of life than the *average duration* or *expectancy of life* measured in years It is appropriate to append a few remarks with respect to the calculation of this measure in the situation here considered If we had a survival curve calculated that traced the percentage surviving for the entire period of life of the group concerned this curve would begin with 100 per cent at the time of origin and proceed showing with the passing years the decreasing percentage remaining at various time periods afterward till there was none left and the per cent surviving would be zero To obtain such a curve at least a representative number of the individuals need to have been traced for a sufficiently long period to the point where the death rate at the end of their traced period is 100 per cent With such a curve established we can calculate the average duration by what amounts to the usual procedure of striking an average The area under the curve is the total person years lived and this divided by the number we started with 100 in the present case gives the average duration of life In terms of a formula if $l_0=100$ is the number we start with and l_1 l_2 l_3 and so forth are the numbers surviving at the successive years thereafter to l_r the last survivors (that is those surviving at the beginning of the last year after which none is left) then the average duration or expectancy is given by the formula

$$e=\frac{50+l_1+l_2+l_3+\quad+l_r}{100}$$

It is essential that the survival curve be traced to its end point of zero survivors if this calculation is to be carried out If we have traced the curve for only say 15 years and at that point the percentage survival rate is 45 per cent then manifestly we cannot calculate the average expectancy for we do not know what the curve will be like after the 15 year period It is seldom that the survival curve is traceable to the point of zero survivors and although we have persevered in some of our own series for a length of survival to 25 years after operation we have yet to calculate our first average expectancy Actually we have outlined the method of calculating this average in order to point out its difficulty rather than because of its practical use as a measure of mortality in a cancerous group

One of the most flagrant *faux pas* committed in the medical literature dealing with duration of life for defined medical conditions is the calculation and presentation of the average duration of life this figure calculated from the records of only those patients for whom there is a report of death with the time of death recorded The argument seems to be We are trying to find the average duration of

life we do not know how long a person has lived until he has died. Since we wish to report only what we know, we must deal with only those regarding whom the time of death is available." So far as reporting the facts regarding these specific patients is concerned, the argument is invulnerable. But the implication is always that the given figure is representative of the duration of life of the entire disease-bearing group considered. Otherwise it is meaningless. No one wants to know the duration for just some specified individuals. Now it ought to be clear that if we take up at any particular time only those patients already dead, we are dealing with a selected group specifically for shortness of life. If we are making an investigation of patients who underwent operation, say, 5 years prior to investigation, it is patent that no patient dead can have lived for more than 5 years, and the calculated average for such patients *must* be less than 5 years. The longer the time elapses to investigation, the longer will appear the length of life!

The *median* length of life is another sort of average that does not have the difficulty of calculation mentioned for the mean duration of life; that is, it does not require tracing the survival curve to its ultimate zero level, and it is frequently, though not always, possible to estimate for available data. The median duration is the length of time required for 50 per cent of the individuals to have died. It is determined from the graph of the survival curve by noting the place on the time scale corresponding to where the curve crosses the 50 per cent level. The median years of survival estimated this way are shown in Figure 37.2.

Another erroneous calculation sometimes seen issued from the most respectable of statistical quarters is the calculation of survival rates for treated patients estimated as from *time of onset of the disease* instead of from time of treatment. The time of onset is estimated from the patient's recollection and is frequently unreliable, but this is not the present point. Suppose the time of onset were accurately and precisely known for each of the treated cases. If we consider, say, the patients whose onset was 1 year before treatment, then all those who might have had treatment a year after onset but who died before this time are not in the records—only the survivors are. Similarly, patients whose onset was 2 years before operation will have no deaths recorded in the 2 years after onset, and so forth. In short, the *recorded* death rate of a group hypothetically followed from onset for each year following onset is *zero* until treatment, because the patients who died before the time of treatment are not at hand to be recorded. To obtain survival rates from onset one would need to deal with an entire community's cancer records retrospectively, in a situation where one had the date of onset and could be sure to obtain all records of death from the cancer. *If we have only a group of patients who have been treated, survival rates cannot be calculated retrospectively as from the time of onset.* Survival rates can be calculated only from time of treatment or some subsequent point. However, the information regarding time of onset that is available in the records can usefully be given separately in the form of statistics regarding duration of the disease. Thus one might report that the 5 year survival rate was 65 per cent and that the average duration of the disease prior to treatment was 3.6 years.

Bibliographies

CHAPTER 1

1 Bauer K H *Das Krebsproblem* Berlin Springer Verlag 1949 p 648

2 Dunn J E and S W Greenhouse Cancer Diagnostic Tests *Pub Health Publ 9* 1950

3 Homburger F Evaluation of Diagnostic Tests for Cancer *Cancer 2* 143 1950

4 Hueper W C *Occupational Tumors and Allied Diseases* Springfield Ill Charles C Thomas 1942

5 ——— Environmental and Occupational Cancer *Pub Health Rep Suppl 209* 1948 p 68

6 ——— A Methodology of Environmental Cancer Surveys *Pub Health Techn Monograph* 1 1950 p 37

7 ——— Carcinogens and Carcinogenesis *Am J Med 8* 355 1950

8 ——— Environmental Lung Cancer *Indust Med 20* 49 1951

9 ——— Environmental Cancers a Review *Cancer Res 12* 691 1952

10 ——— Age Aspects of Environmental and Occupational Cancers *Pub Health Rep 67* 773 1952

11 Pack G T The Relation of Cancer to Trauma *Compens Med 3* 5 1950

12 Wynder E L Some Practical Aspects of Cancer Prevention *New England J Med 246* 492 538 573 1952

CHAPTER 2

1 Adair F E Factors Relating to the Organization and Conduct of a Special Cancer Institute *Surg Gynec & Obst 64* 504 1937

2 ——— Cancer Clinic in the General Hospital *Hospitals 12* 20 1938

3 Beecham C T and T L Montgomery Organization and Administration of Gynecologic Tumor Clinic With Certain Observations Concerning Therapy *Pennsylvania M J 48* 697 1945

4 Bolin Z E Cancer Clinics in Small Hospitals *California & West Med 45* 409 1936

5 Brunschwig A Organization and Conduct of Tumor Clinic Albert Merritt Billings Hospital University of Chicago *Hosp Coun Bull* 6 12 1943

6 Burnap W L *et al* Fergus Falls Cancer Detection Clinic *Minnesota Med 31* 161 1948

7 Cameron C S *A Cancer Source Book for Nurses* New York The American Cancer Society 1950 pp 56

8 Charlton H R The Westchester Plan A County Method for Cancer Control *Surg Gynec & Obst 52* 533 1931

9 Cockerill E The Role of the Social Service Worker in the Diagnosis and Treatment of Cancer *Bull Am Coll Surgeons 17* 15 1933

10 Committee on Cancer American College of Surgeons *Manual for Registries and Cancer Clinical Activities* 1955

11 Crowell B C The American College of Surgeons and Cancer *Surg Gynec & Obst 52* 625 1931

12 ——— Organization of Cancer Clinics in General Hospitals *Wisconsin M J 31* 373 1932

13 ——— and I G MacDonald Organization and Conduct of Cancer Clinics in General Hospitals *Bull Am Coll Surgeons 24* 84 1939

14 ——— Organization of Cancer Clinics and Other Cancer Activity of American College of Surgeons *Proc Education Anderson Hospital Cancer Research* pp 47 ff 1944

15 ——— and C F Branch Cancer Clinics Cancer Diagnostic Clinics Cancer Detection Centers Minimum Standards and Their Amplification *Bull Am Coll Surgeons 32* 131 1947

16 Cutler M Organization of Tumor Clinic in a General Hospital *Radiology 19* 203 1932

17 Dailey U G Tumor Service of Provident Hospital Chicago *Hosp Coun Bull 6* 12 1943

18 Davison R O Saskatchewan s Programme for Cancer Control *Canad J Pub Health 24* 566 1933

19 Davidson T C Atlanta Cancer Clinic *Hosp Management 44* 22 1937

20 Dix A A J and J H Gilligan The Head and Neck Tumor Service at Episcopal Eye Ear and Throat Hospital *M Ann District of Columbia 19* 589 1950

21 Dorn H F and S J Cutler *Morbidity from Cancer in the United States* Public Health Monograph No 29 Washington D C U S Government Printing Office July 1955

22 Dukes G A Administration of a Cancer Clinic in a General Hospital *Bull Am Coll Surgeons 15* 3 1931

23 Ewing J R B Greenough and J C A Gerster Medical Service Available for Cancer Patients in the United States Suggestions for Its Improvement *J A M A 92* 165 1929

24 Ewing J The Cancer Research Hospital *New York M J* December 27 1913

25 ——— Cancer as a Public Health Problem *Public Health Rep 44* 2093 1929

26 ——— Cancer Institutes *Surg Gynec & Obst 52* 522 1931

27 Federal Security Agency Public Health Service Publication No 14 *Cancer Services and Facilities in the United States 1950* Washington D C U S Government Printing Office

28 Ellbrack H R Norwegian American Hospital Tumor Clinic *Hosp Coun Bull* 6 11 1943

29 Foster R J and M M Yaberc Cancer

Bibliographies

CHAPTER 1

1 Bauer K H *Das Krebsproblem* Berlin Springer Verlag 1949 p 648

2 Dunn J E and S W Greenhouse Cancer Diagnostic Tests *Pub Health Publ 9* 1950

3 Homburger F Evaluation of Diagnostic Tests for Cancer *Cancer 2* 143 1950

4 Hueper W C *Occupational Tumors and Allied Diseases* Springfield Ill Charles C Thomas 1942

5 ——— Environmental and Occupational Cancer *Pub Health Rep Suppl 209* 1948 p 68

6 ——— A Methodology of Environmental Cancer Surveys *Pub Health Techn Monograph* 1 1950 p 37

7 ——— Carcinogens and Carcinogenesis *Am J Med 8* 355 1950

8 ——— Environmental Lung Cancer *Indust Med 20* 49 1951

9 ——— Environmental Cancers a Review *Cancer Res 12* 691 1952

10 ——— Age Aspects of Environmental and Occupational Cancers *Pub Health Rep 67* 773 1952

11 Pack G T The Relation of Cancer to Trauma *Compens Med 3* 5 1950

12 Wynder E L Some Practical Aspects of Cancer Prevention *New England J Med 246* 492 538 573 1952

CHAPTER 2

1 Adair F E Factors Relating to the Organization and Conduct of a Special Cancer Institute *Surg Gynec & Obst 64* 504 1937

2 ——— Cancer Clinic in the General Hospital *Hospitals 12* 20 1938

3 Beecham C T and T L Montgomery Organization and Administration of Gynecologic Tumor Clinic With Certain Observations Concerning Therapy *Pennsylvania M J 48* 697 1945

4 Bolin Z E Cancer Clinics in Small Hospitals *California & West Med 45* 409 1936

5 Brunschwig A Organization and Conduct of Tumor Clinic Albert Merritt Billings Hospital University of Chicago *Hosp Coun Bull* 6 12 1943

6 Burnap W L *et al* Fergus Falls Cancer Detection Clinic *Minnesota Med 31* 161 1948

7 Cameron C S *A Cancer Source Book for Nurses* New York The American Cancer Society 1950 pp 56

8 Charlton H R The Westchester Plan A County Method for Cancer Control *Surg Gynec & Obst 57* 533 1933

9 Cockerill E The Role of the Social Service Worker in the Diagnosis and Treatment of Cancer *Bull Am Coll Surgeons 17* 15 1933

10 Committee on Cancer American College of Surgeons *Manual for Registries and Cancer Clinical Activities* 1955

11 Crowell B C The American College of Surgeons and Cancer *Surg Gynec & Obst 52* 625 1931

12 ——— Organization of Cancer Clinics in General Hospitals *Wisconsin M J 31* 373 1932

13 ——— and I G MacDonald Organization and Conduct of Cancer Clinics in General Hospitals *Bull Am Coll Surgeons 24* 84 1939

14 ——— Organization of Cancer Clinics and Other Cancer Activity of American College of Surgeons *Proc Education Anderson Hospital Cancer Research* pp 47 ff 1944

15 ——— and C E Branch Cancer Clinics Cancer Diagnostic Clinics Cancer Detection Centers Minimum Standards and Their Amplification *Bull Am Coll Surgeons 32* 131 1947

16 Cutler M Organization of Tumor Clinic in a General Hospital *Radiology 19* 203 1932

17 Dailey U G Tumor Service of Provident Hospital Chicago *Hosp Coun Bull* 6 12 1943

18 Davison R O Saskatchewan's Programme for Cancer Control *Canad J Pub Health 24* 566 1933

19 Davidson T C Atlanta Cancer Clinic *Hosp Management 44* 22 1937

20 Den A A J and J H Gilligan The Head and Neck Tumor Service at Episcopal Eye Ear and Throat Hospital *M Ann District of Columbia 19* 589 1950

21 Dorn H F and S J Cutler *Morbidity from Cancer in the United States* Public Health Monograph No 29 Washington D C U S Government Printing Office July 1955

22 Dukes G A Administration of a Cancer Clinic in a General Hospital *Bull Am Coll Surgeons 15* 3 1931

23 Ewing J R B Greenough and J C A Gerster Medical Service Available for Cancer Patients in the United States Suggestions for Its Improvement *J A M A 92* 165 1929

24 Ewing J The Cancer Research Hospital *New York M J* December 27 1913

25 ——— Cancer as a Public Health Problem *Public Health Rep 44* 2093 1929

26 ——— Cancer Institutes *Surg Gynec & Obst 52* 522 1931

27 Federal Security Agency Public Health Service Publication No 14 *Cancer Services and Facilities in the United States 1950* Washington D C U S Government Printing Office

28 Fishback H R Norwegian American Hospital Tumor Clinic *Hosp Coun Bull* 6 11 1943

29 Foster R J and M M Yaberg Cancer

Clinic in Small Hospital *Ohio State M J 45* 698 1949
30 FRAZER M M Detroit Women s Cancer Detection Center and Its Relation to General Practitioner *M Woman s J 55* 21 1948
31 GOLDMAN L B Cancer Prevention and Detection Clinic *J A M A 135* 276 1947
32 GREENOUGH R B Cancer Clinics *New England J Med 201* 1287 1929
33 ——— Cancer Clinics *New England J Med 202* 426 1930
34 ——— Tumor Clinic of the Massachusetts General Hospital *Surg Gynec & Obst 52* 529 1931
35 ——— Cancer Clinics and Cancer Services in General Hospitals *Surg Gynec & Obst 60* 441 1935
36 ——— Extension of Tumor Clinic Service to Include Private Patients *Surg Gynec & Obst 64* 497 1937
37 ——— Organization of Tumor Clinic in a General Hospital in G T PACK and E M LIVINGSTON *Treatment of Cancer and Allied Diseases* 1st ed New York Paul B Hoeber Inc 1940 Vol I pp 14 16
38 HENRY C K P Cancer Clinic in General Hospital With Public and Private Patients *Surg Gynec & Obst 64* 699 1937
39 HERRING R A Cancer Service in Approved General Hospitals *Bull Am Soc Control Cancer 17* 2 1935
40 HILLEBOE H E COMMISSIONER OF HEALTH STATE OF NEW YORK *A Manual for Public Health Officers Cancer Control* New York State Department of Health 1952
41 HOFMANN J W Indianapolis City Hospital Cancer Clinic *J Indiana M A 32* 178 1939
42 HOLL E M Successful Cancer Prevention Clinic *M Woman s J 54* 27 1947
43 HOLMES G W Tumor Clinic for Patient of Moderate Means *Radiology 40* 554 1943
44 HUNDLEY J M JR and G E WARD Oncological Clinic of University of Maryland *Bull School Med Univ Maryland 23* 169 1939
45 KELLY J F Role of General Hospital and Its Staff in Care of Cancer Patient With Special Reference to Formation of Tumor Clinics *Hosp Progr 15* 409 1934
46 KENNEY J F How a Tumor Clinic Should Function *Rhode Island M J 25* 181 1942
47 KLOPP C T Warwick Memorial Clinic for Cancer and Allied Diseases *M Ann District of Columbia 16* 41 1947
48 ——— Cancer Prevention or Detection Clinics *M Ann District of Columbia 16* 701 1947
49 KRESS L C and M L LEVIN Experiences and Results in Tumor Clinic Organization in New York State *Radiology 40* 543 1943
50 LAMBERT J H The State Aided Cancer Clinic *Surg Gynec & Obst 64* 508 1937
51 LEE B J The Value of Cancer Diagnostic Clinics *Bull Am Coll Surgeons 15* 16 1931
52 ——— The Obligation of the General Hospital in Providing Better Service for the Cancer Patient *Bull Am Coll Surgeons 17* 13 1933
53 LIDWINA SISTER M Care of Cancer Patient Demands of New Cancer Program on General Hospitals *Hosp Progr 20* 379 1939
54 LOMBARD H L and E J MACDONALD State Aided Cancer Clinics as Seen by the Practicing Physician *New England J Med 205* 949 1931
55 MACDONALD E J The Present Incidence and Survival Picture in Cancer and the Promise of Improved Prognosis *Bull Am Coll Surgeons 32* 1 1948
56 MARTIN C L Value of Tumor Clinics *South M J 31* 1255 1938
57 MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH Cancer Number *The Commonhealth 25* 192 1938
58 MILLAR W M and M LANDEN Tumor Clinic of Cincinnati General Hospital Record of Its First Decade *Ohio State M J 35* 1069 1939
59 MOCK H E Management of Malignancy by Hospital Tumor Group *Hosp Coun Bull 6* 9 1943
60 MORROW A S Cancer Detection Becomes Outpatient Service *Hospitals 22* 44 1948
61 MORTON J J Organization of a Tumor Clinic in a General Hospital *Surg Gynec & Obst 52* 531 1931
62 NEFF J L Nassau County Tumor Clinic *Memphis M J 10* 21 1935
63 NEWELL Q U The Importance of an Organized Cancer Clinic *South M J 29* 212 1936
64 NIX J T Operation of Oscar Allen Tumor Clinic *New Orleans M & S J 89* 75 1936
65 OLSON F A Organization of Hospital Service for Diagnosis and Treatment of Malignancy *Minnesota Med 18* 481 1935
66 Organization of Service for Diagnosis and Treatment of Cancer—Minimum Standard Recommended by Committee on Treatment of Malignant Diseases American College of Surgeons *Surg Gynec & Obst 52* 1178 1931
67 PACK G T Organization of Tumor Clinic in General Hospital *Surg Gynec & Obst 58* 248 1934
68 PALMER E P Cancer Activities of the American College of Surgeons *Communications of the 2nd International Congress of Scientific and Social Campaign against Cancer* Brussels Belgium 1936
69 PEIRCE L C Cancer Number Massachusetts Department of Public Health *The Commonhealth 25* 250 1938
70 PERRY T M The Roper Hospital Cancer Clinic A Review of a Year s Work *J South Carolina M A 33* 73 1937
71 PHILLIPS C Relationship of Pathologist to Tumor Clinic Program *Texas State J Med 43* 617 1948
72 PYE R L Hutchinson Memorial Cancer Detection Clinic *New Orleans M & S J 100* 72 1947
73 ROSAHN P D Tumor Clinic of New Britain General Hospital Organization and Survey of 1939 Experience *Bull Am Coll Surgeons 25* 247 1940
74 SCHAEFER J H A Record System for Cancer Clinics and Cancer Diagnostic Clinics *Bull Am Coll Surgeons 34* 12 1949
75 SCHRAM M W S Organization and Results of Health Maintenance—Cancer Prevention Clinics *J A M A 129* 275 22 1945
76 ——— Organization of Cancer Prevention Clinics *M Officer* (London) *75* 23 1946
77 SIMMONS C C Reference of Hospital

Cases to the Cancer Clinic *Bull Am Coll Surgeons 15* 5 1931

78 ——— The Follow up of Hospital Cases *Bull Am Coll Surgeons 21* 165 1936

79 SIMPSON B T Description of the Cancer Hospital of the State Institute for the Study of Malignant Disease *Surg Gynec & Obst 52* 525 1931

80 SLAUGHTER D P and H W SOUTHWICK Appraisal of Tumor Clinics in Three Metropolitan Hospitals *Bull Am Coll Surgeons 41* 451 1956

81 SMITH H Organizing Tumor Clinic in General Hospital *Mod Hosp 41* 59 1933

82 SPENCER F H *et al* First Year s Operation of Tumor Clinic at Fulton State Hospital *J Missouri M A 32* 59 1935

83 SPIES J W Cancer Organization in France Belgium England Germany and Sweden *Yale J Biol & Med 3* 533 1931

84 TRUEBLOOD D V Personnel of a Tumor Clinic *West J Surg 46* 172 1938

85 UHLMANN E Practical Aspects of Tumor Clinic Management *Radiology 40* 557 1943

86 WANGENSTEEN O H Cancer Clinic in a University Hospital *Surg Gynec & Obst 64* 502 1937

87 WARD G E The Cancer Clinic in Medical and Dental Schools *Arch Phys Therap 17* 622 1936

88 WEAVER C H Diagnostic Cancer Clinic in Private Hospital *Surg Gynec & Obst 62* 424 (2A) 1936

89 ——— Cancer Clinics in Private Hospital *Surg Gynec & Obst 64* 510 (2A) 1937

90 WEBSTER A Prevention Clinics—Step in Cancer Control *J Indiana M A 38* 269 1945

91 WILLIAMS E B Cancer Detection Clinic in the Small Hospital *Illinois M J 97* 58 1950

92 WOLFER J A Role of Surgeon in Tumor Clinic *Radiology 40* 549 1943

93 ——— Patterson Tumor Clinic of Northwestern University and Passavant Memorial Hospital *Hosp Coun Bull 6* 13 1943

CHAPTER 3

1 LOMBARD H L C C FRANSEEN L S SNEGIREFF and E A POTTER Report of the Cancer Detection Center Demonstration in Massachusetts *New England J Med 245* 793 1951

2 Minimum Standard for Cancer Detection Center *Bull Am Coll Surgeons 36* 403 1951

3 Conference on Cancer Detection *Proceedings American Cancer Society* September 1949

4 NACHER Dissertation sur le cancer Besancon 1740 Cited in WOLFF J *Lehre von der Krebskrankheit* Jena Gustaf Fischer 1928 vol 4 p 558

CHAPTER 5

1 BRODERS A C Squamous Cell Epitheliomas of the Lip a Study of Five Hundred and Thirty seven Cases *J A M A 74* 656 1920

2 ——— Squamous Cell Epithelioma of the Skin a Study of 256 Cases *Ann Surg 73* 141 1921

3 ——— Epithelioma of the Genito Urinary Organs *Ann Surg 75* 574 1922

4 ——— Epithelioma of Cavities and Internal Organs of the Head and Neck *A M A Arch Surg 11* 43 1925

5 ——— Cancer s Self Control *Med J and Rec 121* 133 1925

6 ——— Practical Points on the Microscopic Grading of Carcinoma *New York J Med 32* 667 1932

7 EWING J Some Results of Modern Clinical Cancer Research *J Med 16* 15 1935

8 FRATER K A Study of Epithelial Neoplasms of the Urinary Bladder *J Urol 20* 371 1928

9 VON HANSEMANN D Ueber asymmetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung *Arch path Anat 119* 299 1890

10 ——— *Die mikroskopische Diagnose der bosartigen Geschwülste* 2nd ed Berlin Hirschwald 1902

11 HARRINGTON S W Unilateral and Bilateral Carcinoma of the Breast (Including Paget s Disease) Results Three Five Ten Fifteen and Twenty Years After Operation *Minnesota Med 21* 1 1938

12 RANKIN F W and A C BRODERS Factors Influencing Prognosis in Carcinoma of the Rectum *Surg Gynec & Obst 46* 660 1928

13 SCHOTTLANDER J and F KERMAUNER *Zur Kenntnis des Uteruskarzinoms monographische Studie über Morphologie Entwicklung Wachstum nebst Beitragen zur Klinik der Erkrankung* Berlin Karger 1912 763 pp

14 VIRCHOW R L *Die Cellularpathologie in ihrer Begrundung auf Physiologie und pathologische Gewebelehre* Zwanzig Vorlesungen Berlin Hirschwald 1858 440 pp

CHAPTER 6

1 ADAMS GEO The Spontaneous Biopsy *J Nat Cancer Inst 11* 1025 1951

2 AYRE J ERNEST Diagnosis of Preclinical Cancer of the Cervix *J A M A 138* 11 1948

3 ——— Cyto-Diagnosis in Uterine Cancer *Ciba Clinical Symposia 3* 107 1951

4 BARRINGER B S Carcinoma of Prostate *Surg Gynec & Obst 34* 168 1922

5 BEECHAM C T and J EMICH Evaluation of Cervical Biopsy in the Diagnosis of Carcinoma *Am J Obst & Gynec 63* 645 1952

6 BLADY J V Aspiration Biopsy of Tumors in Obscure or Difficult Locations Under Roentgenoscopic Guidance *Am J Roentgenol 42* 515 1939

7 BUCKLEY G E Diagnosis and Treatment of Papillary Adenomas of the Rectum *Am J Surg 75* 365 1948

8 COGSWELL K C L SCHIFF S A SALDI D F RICHFIELD C W KUMPE and E A GALL Needle Biopsy of the Liver *J A M A 140* 385 1949

9 COLE W H D P SLAUGHTER and L J ROSSITER Potential Dangers of Nontoxic Nodular Goiter *J A M A 127* 883 1945

10 COLEY B L *Neoplasms of Bone and Related Conditions* New York Paul B Hoeber Inc 1949 pp 28-40

11 ——— G S SHARP and E B ELLIS Diagnosis of Bone Tumors by Aspiration *Am J Surg 13* 215 1931

12 COLLER F A and R E BERRY Cancer of the Colon *J A M A 135* 1061 1947

13 CRAVER L F and J S BINKLEY Aspira

tion Biopsy of Tumors of the Lung *J Thoracic Surg 8* 436 1939
14 Crowley Robert T and D A Davis A Procedure for Total Biopsy of Doubtful Polypoid Growths of the Lowest Large Bowel Segment *Surg Gynec & Obst 93* 23 1951
15 Guster R P Studies on the Structure and Function of Bone Marrow III Bone Marrow Biopsy *Am J M Sc 185* 617 1933
16 Ellis F Needle Biopsy in the Clinical Diagnosis of Tumors *Brit J Surg 34* 240 1947
17 Eustermann G B The Digestive System *Yearbook of Medicine* Beeson P B J B Anderson G R Minot W B Castle P R Harrison and G B Eustermann (eds) Chicago Year Book Publishers Inc 1949
18 Ferguson R S Prostatic Neoplasms Their Diagnosis by Needle Puncture and Aspiration *Am J Surg 9* 507 1930
19 Foote F Jr and F W Stewart The Anatomical Distribution of Intraepithelial Epidermoid Carcinomas of the Cervix *Cancer 1* 431 1948
20 Gusberg S B Coning Biopsy in the Detection of Early Cancer of the Cervix *Am J Obst & Gynec 61* 276 1951
21 Haagensen Cushman D *Treatment of Cancer and Allied Diseases* Pack G T and E M Livingston (eds) New York Paul B Hoeber Inc 1940 Chap 4 vol 1
22 Hare H F Radiation Treatment of Cancer of the Thyroid *Am J Roentgenol 46* 451 1941
23 Hoffman W J New Technic and Instrument for Obtaining Biopsy Specimens *Am J Cancer 15* 212 1931
24 ——— Punch Biopsy in Tumor Diagnosis *Surg Gynec & Obst 56* 829 1933
25 Huggins C and M A Johnson Cancer of the Bladder and Prostate *J A M A 135* 1146 1947
26 Konzelmann F W *Personal Communication*
27 Kirtland H B Jr Safe Method of Pancreatic Biopsy Preliminary Report *Am J Surg 82* 451 1951
28 Lahey Frank Carcinoma of the Thyroid *Am J Roentgenol 46* 469 1941
29 Martin H and H E Ehrlich Papillary Cystadenoma Lymphomatosum of the Parotid Salivary Gland *Surg Gynec & Obst 79* 611 1944
30 Martin H E and E B Ellis Biopsy by Needle Puncture and Aspiration *Am J Surg 92* 169 1930
31 ——— and F W Stewart The Advantages and Limitations of Aspiration Biopsy *Am J Roentgenol 35* 245 1936
32 Meigs Joe V The Vaginal Smear *J A M A 133* 75 1947
33 Morris A A Use of Smear Technique in the Rapid Histologic Diagnosis of Tumors of the Central Nervou System with a Description of New Staining Method *J Neurosurg 4* 497 1947
34 Morrison M A A Sauwick J Rubinstein Henry Morrison and Leo Loewe Splenic Aspiration *J A M A 146* 1575 1951
35 Norris C M Early Clinical Features of Bronchogenic Carcinoma Illustrative Cases *Dis Chest 14* 198 1948
36 ——— *Personal Communication*
37 Papanicolaou G N *Proceedings* Third Race Betterment Conference 538 New York Hospital Dept of Anatomy Cornell Univ Med College New York 1928
38 ——— and H F Traut Diagnostic Value of Vaginal Smears in Carcinoma of Uterus *Am J Obst & Gynec 42* 193 1941
39 Patterson R and J R Nuttall An Evaluation of the Risk of Biopsy in Squamous Carcinoma *Am J Cancer 37* 64 1939
40 Robertson R C and R P Ball Destructive Spine Lesions Diagnosis by Needle Biopsy *J Bone & Joint Surg 17* 749 1935
41 Rosemond G P W Emory Burnett and J H Hall Value and Limitations of Aspiration Biopsy for Lung Lesions *Radiology 52* 506 1949
42 Rubenstein M A Aspiration of Bone Marrow from the Iliac Crest *J A M A 137* 1281 1948
43 Sardi S A E A Gali C W Kumpe and L Schiff Needle Biopsy of the Liver II Experience with Malignant Neoplasms *Gastroenterology 11* 93 1948
44 Sayago Carlos Aspiration and Surgical Biopsy *Am J Roentgenol 48* 78 1942
45 Scheffey L C Contrasting Methods in Management of Uterine Malignancy *Pennsylvania M J 52* 944 1949
46 ——— and A E Rakoff The Cytology Test for Uterine Cancer *Phila Medicine 43* 435 1947
47 Seybolt J F G N Papanicolaou and W A Cooper Cytology in the Diagnosis of Gastric Cancer *Cancer 4* 286 1951
48 Snyder R E and B L Coley Further Studies on the Diagnosis of Bone Tumors by Aspiration Biopsy *Surg Gynec & Obst 80* 517 1945
49 Stewart F W Diagnosis of Tumors by Aspiration *Am J Path 9* 801 1933
50 Turkel H and F H Bethell Biopsy of Bone Marrow Performed by New and Simple Instrument *J Lab & Clin Med 28* 1246 1943
51 Ulfelder H R M Graham and J V Meigs Further Studies on Cytologic Method in Problem of Gastric Cancer *Ann Surg 128* 422 1948
52 Van Ordstrand H S and T H Lambert The Value of Aspiration Lung Biopsy in Diagnosis *Cleveland Clin Quart 8* 175 1941
53 Volwiler Wade and C M Jones The Diagnostic and Therapeutic Value of Liver Biopsies *New England J Med 237* 651 1947
54 Watson W L Cancer of Paranasal Sinuses *Laryngoscope 52* 22 1942
55 ——— and J L Pool Cancer of the Thyroid *Surg Gynec & Obst 70* 1037 1940

CHAPTER 7

1 Gladstone S A Diagnosis of Early Carcinoma of the Cervix by Sponge Biopsy *New England J Med 241* 48 1949
2 Papanicolaou G N and H F Traut *Diagnosis of Uterine Cancer by the Vaginal Smear* New York Commonwealth Fund 1943
3 ——— and Irena Koprowska Carcinoma in Situ of the Right Lower Bronchus *Cancer 4* 141 1951
4 Wied G L Ueber die cytologische Kar

zinomdiagnostik aus dem Urinsediment *Aerztl Wchnschr 6* 80 1951

CHAPTER 8

1 Ackerman G A R A Knouff and H A Hoster Cytochemical Observations of Cells in Hodgkin s Disease *Cancer Res 11* 233 1951 (abstr)

2 Benitez Soto L El Cultivo de Celulas como Methodo de Investigacion de los Caracteres en las Neoplasias *Rev Mex cir ginec cancer 12* 200 1944

3 Biedermann W and K Hofer Ergebnisse der Zuchtung von menschlichem Xanthomgewebe in vitro *Arch exper Zellforsch 10* 93 1930

4 Bland J O W The Growth of Human Meningiomata in Culture Compared with that of Certain Human Tissues *Arch exper Zellforsch 22* 369 1938 1939

5 ——— and D S Russell Histological Types of Meningiomata and Comparison of Their Behavior in Tissue Culture with That of Certain Normal Human Tissues *J Path & Bact 47* 291 1938

6 Bostick W L The Status of the Search for a Virus in Hodgkin s Disease *in* Viruses as Causative Agents in Cancer *Ann New York Acad Sci 54* 1162 1952

7 De Bruyn W M Het kweeken van weefsels buiten het lichaam II De methode toegepast bij het kankeronderzoek *Vakblad biol 18* 145 1937

8 Buckley R C Tissue Culture Studies of the Glioblastoma Multiforme *Am J Path 5* 467 1929

9 ——— and L Eisenhardt Study of a Meningioma in Supravital Preparations Tissue Culture and Paraffin Sections *Am J Path 5* 659 1929

10 Cameron G Evidence of Retention of Physiological Differentiation in Outgrowing Sheets in Tissue Culture *Anat Rec 100* 646 1948

11 ——— *Tissue Culture Technique* 2nd ed New York Academic Press Inc 1950

12 ——— and R Chambers Neoplasm Studies III Organization of Cells of Human Tumors in Tissue Culture *Am J Cancer 30* 114 1937

13 Chevremont M Le muscle squelettique cultive in vitro Transformation d éléments musculaires en macrophages *Arch de Biol Paris 51* 313 1940

14 Child C M Physiological Dominance and Physiological Isolation in Development and Reconstitution *Arch f Entwcklngsmechn d Organ 117* 21 1929

15 Chlopin N G Ueber in vitro" Kulturen in dem embryonalen Gewebe der Saugetiere *Arch mikr Anat 96* 435 1922, *Klin Wchnschr 1* [illegible] 1922

16 ——— Uber das Wachstum und die Organisationfahigkeit einiger Epithelgewebe ausserhalb des Organismus *Ztschr Krebsforsch 37* 2[illegible] 193[illegible]

17 ——— Uber einige Probleme der modernen [illegible] *Ztschr mikr [illegible]* 34 [illegible] 1933

18 ——— Experimentell [illegible] Untersuchungen uber das [illegible] [illegible] 18 459 1937

19 ——— On the in vitro Cultivation of Peripheral Nerve Fragments *Acad sci URSS Compt rend 23* 175 1939

20 ——— Ueber das Verhalten und des Wachstum peripherer Nerven im Explantat *Arch russes anat 23* 171 223 (Summary) 1940

21 ——— Growth and Transformation of Glio Ependymal Elements of the Spinal Cord Outside the Organism *Akad nauk SSSR Doklady* (Acad sci URSS Compt rend) *41* 87 1943

22 ——— On the Cultivation of Neurogenic Tumors of Man Outside the Organism *Acad sci URSS Compt rend 41* 132 1943

23 Coman D R Human Neoplasms in Tissue Culture *Cancer Res 2* 618 1942

24 ——— Human Neoplasms in Tissue Culture II Observations upon Cells Derived from Peritoneal and Pleural Effusions *Cancer Res 3* 526 1943

25 Cone R E C A Hooks C M Pomerat and G Rose Correlation Studies on Prostatic Fluid Prostatic Tissue and the Testis with Histopathological Papanicolaou Smear and Tissue Culture Technique *Texas Rep Biol & Med 7* 462 1949

26 Cox L C and M L Crandall Studies in the Tissue Culture of Intracranial Tumors *J Path & Bact 45* 477 1937

27 Danchakoff V The Differentiation of Cells as a Criterion for Cell Identification Considered in Relation to the Small Cortical Cells of the Thymus *J Exper Med 24* 87 1916

28 Firket J and H Brabant Importance des reticulo histiocytoses pour les stomatologistes Un cas de reticulo granulomatose maligne de la langue *Arch stomatol Liege 1* 197 1946

29 Fischer A A Three Months Old Strain of Epithelium *J Exper Med 35* 367 1922

30 ——— Die Biologie der Krebszellen in vitro" *Strahlentherapie 50* 79 1934

31 ——— La physiologie de la cellule cancereuse [Summaries in German English Spanish and Italian pp 169 170] *Cancer Brussels 12* 160 1935

32 ——— and R C Parker The Occurrence of Mitoses in Normal and Malignant Tissues in Vitro *Brit J Exper Path 10* 312 1929 *Zentralbl Bakt 97* 328 1930 *Biol Abstr 5* No 28163 1931

33 Fischer E R N Kaufman and E J Mason Hemangiopericytoma Histologic and Tissue Culture Studies *Am J Path 28* 653 1952

34 Geddes I Contributo alla diagnosi dei sedimenti neoplastici mediante la cultura *in vitro Cancro 3* 1[illegible]6 1932 (Turin)

35 Gey G O W D Coffman and M T Kubicek Tissue Culture Studies of the Proliferative Capacity of Cervical Carcinoma and Normal Epithelium *Cancer Res 12* 264 1952

36 ——— and M K Gey Maintenance of Human Normal Cells and Tumor Cells in Continuous Culture I Preliminary Report Cultivation of Mesoblastic Tumors and Normal Tissues and Notes on Methods of Cultivation *Am J Cancer 27* 45 1936

37 Glatthaar E Ueber Versuche zur cytologischen Differenzierung des atypischen Portioepithels mit Hilfe von Gewebezuchtung und Phasenkontrastmikroskopie *Schweiz med Wchnschr* [illegible] 0 1948

38 ——— L emploi de la culture de tissus et de la microscopie à différence de phase pour le jugement pronostiqué des lésions précan céreuses du col uterin *Bruxelles méd 29* 1611 1949

39 Grand C G Neoplasm Studies IV Clas matosis in the Melanoblast *Am J Cancer 33* 394 1938

40 ——— Tissue Culture Studies of Lymph Nodes of Hodgkin s Disease *Cancer Res 7* 49 1947

41 ——— Cytoplasmic Inclusions and the Characteristics of Hodgkin s Diseased Lymph Nodes in Tissue Culture *Cancer Res 9* 183 1949

42 ——— and G Cameron Increased Ac tivity of the Hodgkin s Disease Factor by Serial Transplants in Tissue Culture *Cancer Res 6* 502 1946

43 ——— and ——— Tissue Culture Studies of Pigmented Melanomas Fish Mouse and Human The Biology of Melanomas *N Y Acad Sci Special pub 4* 171 1948

44 ——— R Chambers and G Cameron Neoplasm Studies I Cells of Melanoma in Tissue Culture *Am J Cancer 24* 36 1935

45 Haagensen C D and A P Stout Syno vial Sarcoma *Ann Surg 120* 826 1944

46 Harrison R G Observations on the Liv ing Developing Nerve Fiber *Proc Soc Exp Biol & Med 4* 140 1906 07 *Anat Rec 1* 116 1906 08

47 Heim K Uber das Verhalten menschlicher Gewebe und Geschwulste im Explantations ver such *Klin Wchnschr 5* 2141 1926 *Munchen med Wchnschr 73* 1545 1926

48 Hengstmann H Zur cytologischen Diag nostik von carcinomatosen Pleura und Peritoneal ergussen durch Zellkulturen *Ztschr Klin Med 139* 58 1941

49 Hirschberg E M R Murray F R Peterson J Kream R Schafranek and J L Pool Enzymatic Deamination of 8 azaguanine in Normal Human Brain and in Glioblastoma Multiforme *Cancer Res 13* 153 1953

50 Hofer K Beobactungen an Gewebskul turen menschlicher Hautkarzinome kontrolliert durch kinematographische Zeitrafferaufnahmen *Arch exper Zellforsch 16* 139 1934

51 Hoster H A and M B Dratman Hodgkin s Disease 1832 1947 (Part I II) *Can cer Res 8* 1 1948

52 ——— J W Riddle M D Heise M S Flower M E Shanley B J Welshimer and C A Doan Studies in Hodgkin s Syndrome VI Clinical and Etiological Studies *Ohio Med J 43* 721 1947

53 Ivers J B and C M Pomerat Observa tions on Cells from Ascitic Fluid Cultured in Vitro *Texas Rep Biol & Med 5* 92 1947

54 Juba A Geschwulste des Zentralnerven systems (Meningeom Neurinom) in der Gewe bekultur [Summaries in English and French pp 335 336] *Monatschr Psychiat u Neurol 113* 321 1947

55 Kay S W P Callahan Jr M R Mur ray H T Randall and A P Stout Glomus Tumors of the Stomach *Cancer 4* 726 1951

56 Kredel F L Tissue Culture of Intra cranial Tumors With a Note on the Meningi omas *Am J Path 4* 337 1928

57 ——— Intracranial Tumors in Tissue Cul ture *Arch Surg 18* 2008 1929

58 Krontowski A A Methode der Isolierung von Tumoren innerhalb und ausserhalb des Organismus [Summary p 193] *Voprosy onkol 1* 188, 1928 *Ztschr Krebsforsch 29* 89 1929

59 Layton L L and D R Frankel La beled Inorganic Sulfate in the Diagnosis of Car tilaginous Tumors and Their Metastases *Cancer 2* 1089 1949

60 Lipchina I P Eksplantatsiia opucholei meningo sosudistogo riada [Explantation of Tu mors of Meningo Vascular Series] *Voprosy neurokhir 5 (No 3)* 64 1941

61 Lund T M Om forsøg paa dyrkning af maligne menneskesvulster in vitro Forel øbig meddelelse *Hospitalstid 72* 1015 1929

62 de Lustig E Sacerdote and F Schajo wicz Cultivos de Tejido de Tumor Giganto celular de los Huesos Contribución a la His o génesis de la Celula Gigante (Nota previa) *Rev ortop y traumatol 14* 134 1944 1945

63 Maximow A A Untersuchungen über Blut und Bindegewebe VII Ueber "in vitro Kulturen von lymphoidem Gewebe des erwach senen Saugetierorganismus *Arch mikr Anat 96* 494 1922

64 ——— Untersuchungen uber Blut und Bindegewebe VIII Die zytologischen Eigen schaften der Fibroblasten Retikulumzellen und Lymphozyten des lymphoiden Gewebes ausser halb des Organismus ihre genetischen Wechsel beziehungen und prospektiven Entwicklungspoten zen *Arch mikr Anat 97* 283 1923

65 ——— Relation of Blood Cells to Con nective Tissues and Endothelium *Physiol Rev 4* 533 1924

66 ——— Tissue Cultures of Young Mam malian Embryos Carnegie Inst Wash *Contrib Embryol (No 80) 16* 47 1925

67 Mayer A and K Heim Uber Gewebe zuchtung *Zentralbl Gynak 50* 2688 1926

68 Murray M R Demonstration of Schwan nian Origin of Tumors of the Nerve Sheaths *Arch Neurol & Psychiat 42* 1175 1939

69 ——— Comparative Data on Tissue Cul ture of Acoustic Neurilemomas and Meningiomas *J Neuropath & Exper Neurol 1* 123 1942

70 ——— Cultural Characteristics of Three Granular Cell Myoblastomas *Cancer 4* 857 1951 (Festschrift for Arthur Purdy Stout)

71 ——— and A P Stout Schwann Cell versus Fibroblast as the Origin of the Specific Nerve Sheath Tumor Observations upon Normal Nerve Sheaths and Neurilemomas in vitro *Am J Path 16* 41 1940

72 ——— and ——— The Glomus Tumor Investigation of its Distribution and Behavior and the Identity of its Epithelioid Cell *Am J Path 18* 183 1942

73 ——— and ——— Demonstration of the Formation of Reticulin by Schwannian Tu mor Cells in vitro *Am J Path 18* 585 1942

74 ——— and ——— Characteristics of Human Schwann Cells in vitro *Anat Rec 84* 275 1942

75 ——— and ——— Neuroepithelioma of the Radial Nerve with a Study of its Behaviour in vitro *Rev canad biol 1* 651 1942

76 ——— and ——— Characteristics of a Liposarcoma Grown in vitro *Am J Path 19* 751 1943

77 ——— and ——— Cultural Character

istics of a Hemangioendothelioma *Am J Path* *20* 277 1944

78 ———, ——— and I A Pogogeff Synovial Sarcoma and Normal Synovial Tissue Cultivated in vitro *Ann Surg* *120* 843 1944

79 ——— and ——— Distinctive Characteristics of the Sympathicoblastoma Cultivated in vitro A Method for Prompt Diagnosis *Am J Path* *23* 429 1947

80 ——— and ——— Tissue Cultures from Human Adult Thymus Glands *Anat Rec* *100* 67 (abstract Supplement) 1948

81 ——— and ——— A Sympathetic Ganglioneuroma Cultivated in vitro *Cancer* *1* 242 1948

82 ——— and ——— Cultural Characteristics of Some Human Tumors Derived from Nerve Cells at Various Stages of Differentiation *Acta Unio internat contra cancrum* *6* 1007 1950

83 ——— and ——— *Unpublished observations*

84 Parker R C *Methods of Tissue Culture* 2nd ed New York Paul B Hoeber Inc 1950

85 Pierce M I Cultures of Leukemic Blood Leukocytes *A M A Arch Path* *14* 295 1932 *Zentralbl allg Path* *57* 367 1933

86 Pinkus H The Isolation of Pure Strains of Cells from Human Tumors II Growth Characteristics of a Sarcoma and Two Brain Tumors in Tissue Culture Conclusions *Am J Cancer* *29* 25 1937

87 Pogogeff I A and M R Murray Form and Behavior of Adult Mammalian Skeletal Muscle in vitro *Anat Rec* *95* 321 1946

88 Pomerat C M Tissue Culture Methods *Methods in Medical Research* *4* 198 292 1951 The Year Book Publishers Inc Chicago [Murray M R Tissue Culture Procedures in Medical Installations pp 211 216]

89 ——— Motion Picture Studies of Living Papilloma of the Breast and Breast Cancer *Texas Rep Biol & Med* *10* 217 1952

90 Russell D S and J O W Bland A Study of Gliomas by the Method of Tissue Culture *J Path & Bact* *36* 273 1933

91 ——— and ——— Further Notes on the Tissue Culture of Gliomas With Special Reference to Bailey s Spongioblastoma *J Path & Bact* *39* 375 1934

92 Sano M E Kinetic Pathology (Abstract) *Anat Rec* *106* 243 1950

93 ——— and C T Bello Diagnostic Value of Differentiating Between Morphologically Identical Cells by Tissue Culture *Am J Med* *6* 509 1949 Excerpta med Sec *5 Gen Path* *3 No 813* 1950 (Abstract)

94 ——— and L W Smith Tissue Culture as a Diagnostic Aid in the Identification of Atypical Tumors *A M A Arch Path* *30* 504 1940

95 ——— E Weiss and E S Gault Pleural Mesothelioma *J Thoracic Surg* *19* 783 1950

96 Santesson L Characteristics of Epithelial Mouse Tumour Cells in vitro and Tumour Structures in vivo a Comparative Study *Acta path et microbiol scandinav Suppl* *24* 5 237 1935

97 Sherrington C S *The Integrative Action of the Nervous System* New Haven Yale University Press 1947

98 Stout A P Rhabdomyosarcoma of the Skeletal Muscles *Ann Surg* *123* 447 1946

99 ——— Hemangiopericytoma *Cancer* *2* 1027 1949

100 ——— Solitary Fibrous Mesothelioma of the Peritoneum *Cancer* *3* 820 1950

101 ——— and G M Himadi Solitary (Localized) Mesothelioma of the Pleura *Ann Surg* *133* 50 1951

102 ——— and M R Murray Hemangiopericytoma a Vascular Tumor Featuring Zimmermann s Pericytes *Ann Surg* *116* 26 1942

103 ——— and ——— Localized Pleural Mesothelioma Investigation of Its Characteristics and Histogenesis by Method of Tissue Culture *A M A Arch Path* *34* 951 1942

104 Timofeevskii A D S V Benevolenskaya and B B Vorshavskaya Cultivation of Human Malignant Growths *Les problemes d oncol* *10* 22 1936 (Abstract) *Am J Cancer* *31* 507 1937

105 ——— K voprosu o sposobnosti kletok zlokachestvennykh opukholei k diferentsirovka Opyt kultivirovania zlokachestvennoi rabdomioblastomy [Question of Capacity of Cells of Malignant Neoplasms for Differentiation Culture of Malignant Rhabdomyoblastoma] *Vrach delo* *20* 569 1938

106 ——— Continuous Cultures of Tumours of Man Dlitelnye kultury opukholei cheloveka [Summary in Russian p 25 28] *Acta med URSS* *2* 13 1939

107 ——— Dalshi sposterezhennia nad trivalimi kulturami zloiakisnykh pukhlin liudini Les observations ulterieures des cultures de longue duree des tumeurs malignes de l homme [Summaries in Russian and French pp 1277 1279] *Med zh* *9* 1273 1940

108 ——— Tumor Origin as Determined by Tissue Culture *Am Rev Soviet Med* *4* 106 1946 1947

109 ——— Eksplantatsiia opukholei cheloveka [Explantation of Human Tumors] Moskva *Akad med nauk SSSR* 1947 160 pp

110 Weiss P The Problem of Specificity in Growth and Development *Yale J Biol & Med* *19* 235 1947

111 ——— and H Wang Transformation of Adult Schwann Cells into Macrophages *Proc Soc Exp Biol & Med* *58* 273 1945

112 Weitzmann G Epithel und Karzinom des erwachsenen Menschen in vitro *Arch exper Zellforsch* *22* 347 1938

113 Werner K C Landschutz and G A Kausche Relations Between Lymphogranulomatosis and Reticulum Cell Sarcoma Studies on Tissue Culture *Ztschr Krebsforsch* *57* 672 1951

114 Winkler Junius E A Peculiar Mode of Growth of an Astrocytoma in vitro *Acta Neerland morphol normal path* *6* 106 1948 1949

115 Wolf A and W M Honeyman Appearance of Meningioma in Culture *Bull Neurol Inst N Y* *6* 569 1937

116 Zimmermann K W Der feinere Bau der Blutcapillaren *Ztschr Anat* *68* 29 1923

CHAPTER 9

1 Adolph F Water Metabolism *Ann Rev Physiol* *9* 381 1947

2 Arieli I M Internal Balance of Plasma

Protein in Surgical Patients *Surg Gynec & Obst 92* 405 1951
3 ——— Effects of a Water Load Administered to Patients During the Immediate Postoperative Period the Hypotonic Syndrome *A M A Arch Surg 62* 303 1951
4 ——— Metabolic Alterations Induced by Intra abdominal Operations *Ann Surg 138* 186 1953
5 ——— Chloridorrhea a Syndrome Associated With Diarrhea and Potassium Deficiency *A M A Arch Surg 68* 105 1954
6 ——— The Effects of Gastric Anacidity upon the Metabolic Alterations Induced by Gastric Aspiration *Surg Gynec & Obst 98* 213 1954
7 ——— and A J KREMEN Compartmental Distribution of Sodium Chloride in Surgical Patients Pre and Postoperatively *Ann Surg 132* 1009 1950
8 ——— and F A MILLER The Effects of Hypochloremia upon Renal Function in Surgical Patients *Surgery 28* 552 1950
9 ——— and ——— Effects of Abdominal Surgery upon Renal Clearance *Surgery 28* 716 1950
10 ——— G T PACK and C P RHOADS The Influence of Gastric Surgery on the Chemical Composition of the Liver *Ann Surg 116* 924 1942
11 ——— J ABELS G T PACK and C P RHOADS Postoperative Hypoproteinemia and Relationship of Serum Protein Fall to Urinary Nitrogen Excretion *Surg Gynec & Obst 77* 16 1943
12 ——— ——— ——— and ——— The Treatment of Hypochloremia Refractory to the Administration of Sodium Chloride Especially in Patients With Gastrointestinal Cancer *J A M A 123* 23 1947
13 BRAASCH J W Protein Metabolic Response to Trauma *Surg Gynec & Obst 88* 1 1949
14 BROWNE J S V SCHENKER and J A STEVENSON Some Metabolic Aspects of Damage and Convalescence *J Clin Invest 23* 932 1944
15 COLLER F A K N CAMPBELL H H VAUGHN L V IOB and C A MOYER Postoperative Salt Intolerance *Ann Surg 119* 533 1944
16 ——— A V IOB H H VAUGHN N TALDEN and C A MOYER Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively *Ann Surg 122* 663 1945
17 COOKE R E and W E SEGAR A Proposed Mechanism of Extracellular Regulation of Muscle Composition *Yale J Biol & Med 25* 83 1952
18 ——— ——— D B CHEEK F E COLVILLE and D C DARROW The Extrarenal Correction of Alkalosis Associated With Potassium Deficiency *J Clin Invest 31* 798 1952
19 COPE O J B GRAHAM G MIXTER JR and M R BALL Threshold of Thermal Trauma and Influence of Adrenal Cortical and Posterior Pituitary Extracts on the Capillary and Chemical Changes an Experimental Study *A M A Arch Surg 59* 1015 1949
20 ——— I T NATHANSON G M ROURKE and H WILSON Metabolic Observations *Ann Surg 117*·937 1943
21 CUTHBERTSON D P J L MCGIRR and J M ROBERTSON Effect of Fracture of Bone on Metabolism of Rat *Quart J Exper Physiol 29* 13 1939
22 DARROW D C Changes in Muscle Composition in Alkalosis *J Clin Invest 25* 324 1946
23 ——— R SCHWARTZ J F IANUCCI and F COVILLE The Relation of Serum Bicarbonate Concentration to Muscle Composition *J Clin Invest 27* 198 1948
24 ELIEL L P O H PEARSON and F C WHITE Postoperative Potassium Deficit and Metabolic Alkalosis the Pathologic Significance of Operative Trauma and of Potassium and Phosphorus Deprivation *J Clin Invest 31* 419 1952
25 ELKINTON J R A W WINKLER and T S DANOWSKI Transfers of Cell Sodium and Potassium in Experimental and Clinical Conditions *J Clin Invest 27* 74 1948
26 EVANS F I Potassium Deficiency in Surgical Patients Its Recognition and Management *Ann Surg 131*·945 1950
27 ELMAN R *Surgical Care* New York Appleton Century Crofts Inc 1951
28 FOX C L JR J M WINFIELD L B SLOBODY C M SWINDLER and J K LATTIMER Electrolyte Solution Approximating Plasma Concentrations *J A M A 148* 827 1952
29 FREIS E D and J F KENNY Plasma Volume Total Circulating Proteins and Available Fluid" Abnormalities in Preeclampsia and Eclampsia *J Clin Invest 27* 283 1948
30 GAMBLE J L *Chemical Anatomy Physiology and Pathology of Extracellular Fluid A Lecture Syllabus* Cambridge Harvard University Press 1941
31 GAUDINO M and M F LEVITT Influence of the Adrenal Cortex on Body Water Distribution and Renal Function *J Clin Invest 28* 1487 1949
32 GREGERSEN M I and J D STEWART Simultaneous Determination of Plasma Volume with T 1824 and the Available Fluid Volume with Sodium Thiocyanate *Am J Physiol 125* 142 1939
33 HASTINGS A B The Electrolytes of Tissues and Body Fluids *Harvey Lect 36* 91 1941 (1940 1941)
34 LILING M and R GAUNT Acquired Resistance to Water Intoxication *Am J Physiol 144* 571 1945
35 LOCKWOOD J S and H T RANDALL Place of Electrolyte Studies in Surgical Patients *Bull New York Acad Med 25* 228 1949
36 MOORE F D Determination of Total Body Water and Solids With Isotopes *Science 104* 157 1946
37 ——— Adaptation of Supportive Treatment to Needs of the Surgical Patient *J A M A 141* 646 1949
38 ——— and M R BALL *The Metabolic Response to Surgery* Springfield Ill Charles C Thomas 1952
39 MUSSER J H and M M WINTROBE *In* Tice *System of Medicine* Hagerstown Md W F Prior Co 1940 p 795
40 NOBLE R P and M I GREGERSEN Blood Volume in Clinical Shock I Mixing Time and Disappearance Rate of T 1824 in Normal Subjects and in Patients in Shock Determination of Plasma Volume in Man from 10 Minute Sample

J Clin Invest 25 158 1946
41 Oppenheim A G T Pack J C Abels and C P Rhoads Estimation and Significance of Blood Loss During Gastrointestinal Surgery *Ann Surg 119* 865 1944
42 Overman R R T S Hill and Y T Wong Physiological Studies in the Human Malarial Host I Blood Plasma "Extracellular" Fluid Volumes and Ionic Balance in Therapeutic P Vivax and P Falciparum Infections *J Nat Malaria Soc 8* 14 1949
43 Peters J P and D B Van Slyke *Quantitative Clinical Chemistry Methods* Baltimore Williams & Wilkins 1932 vol 2
44 Randall H T D V Habif and J S Lockwood Sodium Deficiency in Surgical Patients and Failure of Urine Chloride as a Guide to Parenteral Therapy *Surgery 28* 182 1950
45 Schales O and S Schales A Simple and Accurate Method for the Determination of Chloride in Biological Fluids *J Biol Chem 140* 879 1941
46 Selye H 'The General Adaptation Syndrome and the Diseases of Adaptation *in Textbook of Endocrinology* Montreal Acta Endocrinologica Inc 1949
47 Solomon A K I S Edelman and S Soloway The Use of the Mass Spectrometer to Measure Deuterium in Body Fluids *J Clin Invest 29* 1311 1950
48 Stewart J D and G M Rourke On the Measurement of Extracellular Fluid Volume With Thiocyanate and Body Fluid Analyses in 33 Normal Individuals *J Lab & Clin Med 26* 1383 1941
49 ——— and ——— The Effects of Large Intravenous Infusions on Body Fluid *J Clin Invest 21* 197 1942
50 Wangensteen O H Controlled Administration of Fluid to Surgical Patients Including Description of Gravimetric Methods of Determining Status of Hydration and Blood Loss During Operation *Minnesota Med 25* 783 1942
51 ——— Care of the Patient Before and After Operation *New England J Med 236* 121 1947
52 Weech A A C I Snelling and E Goettsch Relation Between Plasma Specific Gravity and Edema in Dogs Maintained on Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis *J Clin Invest 12* 193 1933
53 Weichselbaum T E Determination of Proteins in Blood Serum and Plasma *Am J Clin Path 10* 40 1946 (Tech Section)
54 Weisberg H F *Water Electrolyte and Acid Base Balance* Baltimore Williams & Wilkins Company 1953
55 Whipple G H and S C Madden Hemoglobin Plasma Protein and Cell Protein—Their Interchange and Construction in Emergencies *Medicine 23* 215 1944
56 Wilkinson A W B H Billing G Nagy and C P Stewart Excretion of Sodium and Chloride After Surgical Operations *Lancet 1* [illegible] 1949
57 ——— ——— ——— and ——— Excretion of Potassium After Partial Gastrectomy *Lancet 2* 135 1950
58 Yannet H and D C Darrow The Effect of Depletion of Extracellular Electrolytes on the Chemical Composition of Skeletal Muscle Liver and Cardiac Muscle *J Biol Chem 134* 721 1940
59 Zimmerman B Adrenal Function in Surgical Patients *Bull Univ Minnesota Hosp 21* 439 1950

CHAPTER 10

1 Allen A W R R Linton and G A Donaldson Venous Thrombosis and Pulmonary Embolism *J A M A 128* 397 1945
2 Allen E V E A Hines Jr W F Kvale and N W Barker The Use of Dicumarol as an Anticoagulant Experience in 2307 Cases *Ann Int Med 27* 371 1947
3 Armbrust C A Jr and S A Levine Paroxysmal Ventricular Tachycardia a Study of 107 Cases *Circulation 1* 28 1950
4 Austrian R J H McClement A D Renzetti Jr K W Donald R L Riley and A Cournand Clinical and Physiologic Features of Some Types of Pulmonary Diseases with Impairment of Alveolar Capillary Diffusion *Am J Med 11* 667 1951
5 Baker D V Jr R Warren J Homans and D Littmann Pulmonary Embolism Evaluation of a Policy for Prophylaxis and Therapy *New England J Med 242* 923 1950
6 Baldwin E deF A Cournand and D W Richards Jr Pulmonary Insufficiency Physiological Classification Clinical Methods of Analysis Standard Values in Normal Subjects *Medicine 27* 243 1948
7 ——— ——— and ——— Pulmonary Insufficiency Study of 122 Cases of Chronic Pulmonary Emphysema *Medicine 28* 201 1949
8 Barach A L The Treatment of Anoxia in Clinical Medicine *Bull New York Acad Med 26* 370 1950
9 Barnard F G Treatment of Severe Singultus *Am J Surg 77* 230 1949
10 Beck C S and H J Rand Cardiac Arrest During Anesthesia and Surgery *J A M A 141* 1230 1949
11 Bell E T Incidence of Gangrene of Extremities in Non Diabetic and in Diabetic Persons *A M A Arch Path 49* 469 1950
12 Berenson G S and G E Burch The Response of Patients With Congestive Heart Failure to a Rapid Elevation in Atmospheric Temperature and Humidity *Am J M Sc 223* 45 1952
13 Bickerman H A and C J Beck Pressure Breathing With Oxygen and Helium Oxygen in Pulmonary Edema and Obstructive Dyspnea *Bull New York Acad Med 26* 410 1950
14 Blakemore A H Portacaval Shunt for Portal Hypertension Follow up Results in Cases of Cirrhosis of the Liver *J A M A 145* 1335 1951
15 Blodgett J S Early Ambulation Following Surgical Procedures *Bull New York Acad Med 25* 176 1949
16 Blumgart H L and M D Altschule *Clinical Significance of Cardiac and Respiratory Adjustments in Chronic Anemia* *Blood 3* 329 1948
17 Boyce F F and E M McFetridge Studies of Hepatic Function by the Quick Hippuric Acid Test III Various Surgical States

A M A Arch Surg 37 443 1938
18 Bradley S E Medical Progress The Pathogenesis of Renal Insufficiency New England J Med 233 498 1945
19 Brannon E S A J Merrill J V Warren and E A Stead Jr The Cardiac Output in Patients With Chronic Anemia as Measured by the Technique of Right Atrial Catheterization J Clin Invest 24 332 1945
20 Burchell H B Cardiac Manifestations of Renal Disease Including Pulmonary Edema M Clin North America 35 1083, 1951
21 Callaway J J and V A McKusick Carbon Dioxide Intoxication in Emphysema Emergency Treatment by Artificial Pneumoperitoneum New England J Med 245 9 1951
22 Chamberlain J M and C F Daniels Management of Civilian Injuries of the Chest New York J Med 51 1908 1951
23 Chapman E M and R R Linton Mode of Production of Pulmonary Emboli J A M A 129 196 1945
24 ——— and R D Evans Treatment of Hyperthyroidism With Radioactive Iodine J A M A 131 86 1946
25 Christensen E M and E G Gross Analgesic Effects in Human Subjects of Morphine Meperidine and Methadon J A M A 137 594 1948
26 Clawson B J and E T Bell Incidence of Fatal Coronary Disease in Non Diabetic and in Diabetic Persons A M A Arch Path 48 105 1949
27 Cole S L and J N Sugarman Cerebral Manifestations of Acute Myocardial Infarction Am J M Sc 223 35 1952
28 Collens W S and L C Boas The Modern Treatment of Diabetes Mellitus Including Practical Procedures and Precautionary Measures Springfield Ill Charles C Thomas 1946
29 Collins V J Anesthetic Management of the Cardiac Patient Yale J Biol & Med 19 979 1947
30 Comroe J H Jr and A B Botelho The Unreliability of Cyanosis in the Recognition of Arterial Anoxemia Am J M Sc 214 1 1947
31 ——— Interpretation of Commonly Used Pulmonary Function Tests Am J Med 10 356, 1951
32 Crafoord C Preliminary Report on Postoperative Treatment With Heparin as a Preventive of Thrombus Acta chir scandinav 79 407 1937
33 Culver G A H P Makel, and H K Beecher Frequency of Aspiration of Gastric Contents by the Lungs During Anesthesia and Surgery Ann Surg 133 289 1951
34 Davidson C S and G J Gabuzda Jr Medical Progress Nutrition and Disease of the Liver New England J Med 243 779 1950
35 De La Chapelle C E and O A Rose The Management of Acute Cardiac Emergencies Circulation 4 764 1951
36 DeTakats G Anticoagulant Therapy in Surgery J.A.M A 142 527 1950
37 Dock W The Clinical Significance of Some Peculiarities of the Circulation in the Kidneys Liver Lungs and Heart New England J Med 236 773 1947
38 Draper A J The Cardio Inhibitory Carotid Sinus Syndrome Ann Int Med 32 700 1950
39 Durant T M Nutritional Factors in Cardiac Disease Ann Int Med 35 397 1951
40 Earle D P Jr Renal Function Tests in the Diagnosis of Glomerular and Tubular Disease Bull New York Acad Med 26 47 1950
41 Editorial Cardiac Contraindications to Surgical Procedures New England J Med 241 282 1949
42 ——— Action of Lipotrophic Substances in Liver Disease as Measured by Radioactive Phosphorus J.A.M.A 144 1566 1950
43 ——— Alterations in Normal Bacterial Flora of Man and Secondary Infections During Antibiotic Therapy Second report by the Committee on Public Health Relations of the New York Academy of Medicine Am J Med 11 665 1951
44 Eliel L P O H Pearson, and R W Rawson Postoperative Potassium Deficit in Metabolic Alkalosis New England J Med 243 471 1950
45 Ellenberg M and K E Osserman The Role of Shock in the Production of Central Liver Cell Necrosis Am J Med 11 170 1951
46 Ellis L B, J G Mebane G Maresh H N Hultgren and R A Bloomfield The Effect of Myxedema on the Cardiovascular System Am Heart J 43 341 1952
47 Eversole U H Complications of Spinal Anesthesia S Clin North America 30 693 1950
48 Felder L A Mund and J G Parker Liver Function Tests in Chronic Congestive Heart Failure Circulation 2 286 1950
49 Finkbeiner J F F Wroblewski and J S LaDue Major Surgery in Patients With Chronic Auricular Fibrillation New York J Med 54 1175 1954
50 Flippin H F W V Matteucci N H Schimmel and W P Boger Aureomycin Chloramphenicol and Penicillin in Treatment of Bacterial Pneumonia J.A.M.A 147 918 1951
51 Fowler N O Jr Thrombo-embolism a Survey of Recent Literature Angiology 1 257 1950
52 Fraser H F A Wikler, A J Eisenman and H Isbell Use of n allylnormorphine in Treatment of Methadon Poisoning in Man Report of Two Cases J A M A 148 1205 1952
53 Friedland C K J S Hunt and R W Wilkins Effects of Changes in Venous Pressure upon Blood Flow in the Limbs Am Heart J 25 631 1943
54 Geller W and H J Tagnon Liver Dysfunction Following Abdominal Operation The Significance of Postoperative Hyperbilirubinemia A M.A Arch Int Med 86 908 1950
55 Gilson J S and F R Schemm The Use of Digitalis in Spite of the Presence of Ventricular Tachycardia Circulation 2 278 1950
56 Gluck J L H Gold T Greiner W Modell N T Kwit, S Thickman H L Otto and L J Warshaw Quinidine Sulfate in Propylene Glycol by Intramuscular Injection in Man J.A.M.A 145 637 1951
57 Goodman L and A Gilman The Pharmacological Basis of Therapeutics New York The Macmillan Co 1941
58 Greene C H Progress in Internal Medicine Liver and Biliary Tract A Survey of Tests

for Hepatic Functions the Use of the Hepatic Star in the Differential Diagnosis of Jaundice *A M A Arch Int Med 86* 743 1950

59 Hannigan C A F Wroblewski William H Lewis Jr and J S LaDue Major Surgery in Patients With Healed Myocardial Infarction *Am J M Sc 222* 628 1951

60 Harrison T R *Failure of the Circulation* Baltimore Williams & Wilkins Company 1939

61 Harvey R M M I Ferrer D W Richards Jr and A Cournand Influence of Chronic Pulmonary Disease on the Heart and Circulation *Am J Med 10* 719 1951

62 Hayman J M Jr N P Shumway P Dumke and M Miller Experimental Hyposthenuria *J Clin Invest 18* 195 1939

63 Hesselschwerdt D W and S E Medbury Circulatory Collapse Following the Combined Use of Pituitrin and Pentothal *Anesthesiology 10* 544 1949

64 Hirschfelder A D and V G Haury Effect of Nephrectomy on Duration of Action of Barbitals *Proc Soc Exper Biol & Med 30* 1059 1933

65 Homans J Venous Thrombosis and Pulmonary Embolism *New England J Med 236* 196 1947

66 Howkins J Movement of the Diaphragm After Operation *Lancet 2* 85 1948

67 Huggins C and D M Bergenstal Surgery of the Adrenals *J A M A 147* 101 1951

68 Irwin G W H D Van Vactor and M S Norris Propylthiouracil and Methimazole Therapy *J A M A 149* 1637 1952

69 Jeghers H and H J Bakst The Syndrome of Extrarenal Azotemia *Ann Int Med 11* 1861 1938

70 Joseph S I L R Orkin and E A Rovenstine Clinical Use of Procaine Amide (Pronestyl) During Anesthesia *New York J Med 51* 1827 1951

71 Joslin E P and H F Root *The Treatment of Diabetes Mellitus* Philadelphia Lea and Febiger 1952

72 Kark R M R W Keeton N O Calloway G R Morey R A Chapman and R H Kyle A Rational Basis for the Use of Low Sodium High Protein Diet Therapy in Laennec s Cirrhosis *A M A Arch Int Med 88* 61 1951

73 Keats A S G L D Alessandro and H K Beecher A Controlled Study of Pain Relief by Intravenous Procaine *J A M A 147* 1761 1951

74 Keeton R W W H Cole N O Calloway N Glickman H H Mitchell J Dyniewicz and D Howes Convalescence A Study in the Physiological Recovery of Nitrogen Metabolism and Liver Function *Ann Int Med 28* 521 1948

75 Kinney T D and G K Mallory Cardiac Failure Associated With Acute Anemia *New England J Med 232* 215 1945

76 Kirby W M and D H Coleman Antibiotic Therapy of Friedlander Pneumonia *Am J Med 11* 179 1951

77 Kumpe C W and W B Bean Aortic Stenosis Study of Clinical and Pathological Aspects of 107 Proved Cases *Medicine 27* 139 1948

78 Leiter L The Pathogenesis and Treatment of Uremia *New York J Med 50* 1578 1950

79 Levy R L H G Bruenn and D Kurtz Facts on Disease of Coronary Arteries Based on a Survey of Clinical and Pathologic Records of 762 Cases *Am J M Sc 187* 376 1934

80 Limber C R H G Reiser L C Roettig and G M Curtis Enzymatic Lysis of Respiratory Secretions by Aerosal Trypson *J A M A 149* 816 1952

81 Luisada A A Therapy of Paroxysmal Pulmonary Edema by Antifoaming Agents *Circulation 2* 872 1950

82 Lundy J S *Clinical Anesthesia A Manual of Clinical Anesthesiology* Philadelphia W B Saunders Co 1942

83 Master A M The Two Step Exercise Electrocardiogram A Test for Coronary Insufficiency *Ann Int Med 32* 842 1950

84 ——— S Dack and H L Jaffe Postoperative Coronary Artery Occlusion *J A M A 110* 1415 1938

85 ——— H L Jaffe and W R Dorrance The Treatment of Heart Failure Digitalis and Mercurial Intoxication Penicillin Dicumarol Major Surgery *New York J Med 50* 553 1950

86 McKittrick L S and H F Root Preoperative and Postoperative Treatment of the Patient With Diabetes *A M A Arch Surg 40* 1057 1940

87 Mellinkoff S M P A Tumulty and A M Harvey The Differentiation of Parenchymal Liver Disease and Mechanical Biliary Obstruction *New England J Med 246* 729 1952

88 Menard O J and L M Hurxtal Painless Coronary Thrombosis as a Postoperative Complication *S Clin North America 11* 395 1931

89 Miller M W R Drucker J E Owens J W Craig and H Woodward Jr Metabolism of Intravenous Fructose and Glucose in Normal and Diabetic Subjects *J Clin Invest 31* 115 1952

90 Moon V H Symposium on Inhalation Therapy Anoxia in Clinical Medicine *Bull New York Acad Med 26* 361 1950

91 Moore F D D N Sweeney Jr O Cope R W Rawson and J H Means The Use of Thiouracil in the Preparation of Patients With Hyperthyroidism for Thyroidectomy *Ann Surg 120* 152 1944

92 Negus V E Ciliary Action *Thorax 4* 57 1949

93 Patek A J Jr J Post O D Ratnoff H Mankin and R W Hillman Dietary Treatment of Cirrhosis of the Liver *J A M A 138 543* 1948

94 Petersen L H Some Characteristics of Certain Reflexes Which Modify the Circulation in Man *Circulation 2* 351 1950

95 ——— K I Father and R D Dripps Postural Changes in the Circulation of Surgical Patients as Studied by a New Method for Recording the Arterial Blood Pressure and Pressure Pulse *A M A Arch Surg 131* 23 1950

96 Pfeiffer P H and J S LaDue Major Surgical Operations in the Presence of Bundle Branch Block A Study of the Operative Risk in 59 Patients *Am J M Sc 217* 363 1949

97 Plum F and G D Whedon The Rapid

rocking Bed Its Effect on the Ventilation of Poliomyelitis Patients With Respiratory Paralysis *New England J Med 245* 235 1951
98 POHLE F J Anesthesia and Liver Function *Wisconsin M J 47* 476 1948
99 RHOADS P S C E BILLINGS and V J O CONNOR Antibacterial Management of Urinary Tract Infections *J A M A 148* 165 1952
100 RICHARDS V and F N HARCH Surgical Experiences With Pheochromocytoma *Ann Surg 134* 40 1951
101 ROCHE M G W THORN and A G HILLS The Levels of Circulating Eosinophils and Their Response to ACTH in Surgery *New England J Med 242* 307 1950
102 ROGERS W F WROBLEWSKI and J S LADUE Supraventricular Tachycardia Complicating Surgical Procedures *Circulation 7* 192 1953
103 RUZICKA E R and M J NICHOLSON Cardiac Arrest Under Anesthesia *J A M A 135* 622 1947
104 SCHROEDER H A Renal Failure Associated With Low Extracellular Sodium Chloride The Low Salt Syndrome *J A M A 141* 117 1949
105 SCHWARTZ W B and W M WALLACE Electrolyte Equilibrium During Mercurial Diuresis *J Clin Invest 30* 1089 1951
106 SEGAL M S Medical Progress Inhalation Therapy *New England J Med 230* 456 1944
107 SHAW E C A Study of the Curve Elimination of Phenosulphonphthalein by the Normal and Diseased Kidneys *J Urol 13* 575 1925
108 SPAULDING E H and T G ANDERSON Selection of Antimicrobial Agents by Laboratory Means *J A M A 147* 1336 1951
109 Standards of Effective Administration of Inhalational Therapy Second report by the Committee on Public Health Relations of the New York Academy of Medicine *J A M.A 144* 25 1950
110 STEARNS N S E J CALLAHAN and L B ELLIS Value and Hazards of Intravenous Procaine Amide (Pronestyl) Therapy *J A M A 148* 360 1952
111 TILLETT W S and S SHERRY The Effect in Patients of Streptococcal Fibronolysis (Streptokinase) and Streptococcal Desoxyribonuclease on Fibrinous Purulent and Sanguineous Pleural Exudations *J Clin Invest 28* 173 1949
112 VAN SLYKE D D The Effects of Shock on the Kidney *Ann Int Med 28* 701 1948
113 VOLPITTO P P and J M BROWN Choice of Anesthesia for Patients With Pulmonary Emphysema *J A.M A 142* 897 1950
114 WATSON C J Regurgitation Jaundice Clinical Differentiation of the Common Forms With Particular Reference to the Degree of Biliary Obstruction *J A M A 114* 2427 1940
115 WELLMAN W E and E V ALLEN The Variable Effects of Identical Amounts of Dicumarol on the Prothrombin Values of Different Persons *Proc Staff Meet Mayo Clin 26* 257 1951
116 WEST J R E DEF BALDWIN A COURNAND and D W RICHARDS JR Physiopathologic Aspects of Chronic Pulmonary Emphysema *Am J Med 10* 481 1951
117 WIGGIN S C P SAUNDERS and G A SMALL Medical Progress Resuscitation *New England J Med 241* 370 1949
118 ——— ——— and ——— Medical Progress Resuscitation *New England J Med 241* 413 1949
119 WRIGHT I S *Vascular Diseases in Clinical Practice* Chicago Year Book Publishers 1952
120 WROBLEWSKI F and J S LADUE Myocardial Infarction as a Postoperative Complication of Major Surgey *J A M A 150* 1212 1952

CHAPTER 11

1 BLECH G M *Clinical Electrosurgery* London Oxford Uuniversity Press 1938
2 KELLY H A and G E WARD *Electrosurgery* Philadelphia W B Saunders Co 1932
3 WYETH G A *Surgery of Neoplastic Diseases by Electrothermic Methods* New York Paul B Hoeber Inc 1926

CHAPTER 12

1 ALLEN E V The Clinical Use of Anticoagulants *J.A.M A 134* 323 1947
2 ALLEN J G L O JACOBSON and B S GROSSMAN A Study of Plasma Defect in Patients Whose Bleeding is Temporarily Controlled by Protamine Sulfate or Toluidine Blue *J Lab & Clin Med 33* 1480 1948
3 BALLANCE C A and W A EDMUNDS *A Treatise on the Ligation of the Great Arteries in Continuity* London and New York Macmillan & Co Ltd 1891
4 BATSON O V The Function of the Vertebral Veins and Their Role in the Spread of Metastasis *Ann Surg 112* 138 1940
5 BLAKEMORE A H and J W LORD A Non Suture Method of Blood Vessel Anastomosis *J A M A 127* 685 1945
6 ——— Blood Vessel Anastomosis by Means of a Non Suture Vitallium Tube Method Experimental Studies and Clinical Applications" in *Advances in Surgery* New York Interscience Publishers Inc 1949 vol 1 pp 337 ff
7 BLALOCK A Surgical Procedures Employed and Anatomical Variations Encountered in the Treatment of Congenital Pulmonic Stenosis *Surg Gynec & Obst 87* 385 1948
8 BROOKS B G S JOHNSON and J A KIRTLEY JR Simultaneous Vein Ligation An Experimental Study of the Effect of Ligation of the Concomitant Vein on the Incidence of Gangrene Following Arterial Obstruction *Surg Gynec & Obst 59* 496 1934
9 BUNNELL S *Surgery of the Hand* Philadelphia J B Lippincott Co 1944
10 CALLOW A D and C S WELCH Arterial Anastomosis in Experimental Arterial Injury *Surg Gynec & Obst 90* 77 1950
11 CARLSON H A Obstruction of the Superior Vena Cava An Experimental Study *A M.A Arch Surg 29* 669 1934
12 CARREL A La Technique Operatoire des Anastomoses Vasculare et la Transplantation des Visceres *Lyon med 93* 859 1902
13 CHILD C G III R F MILNES G R HOLSWODE and A L GORE Sudden and Complete Occlusion of the Portal Vein in the

Macaca Mulatta Monkey *Ann Surg 132* 475 1950

14 Cooper F W R I Robertson P C Shea Jr and E W Dennis The Experimental Production of Gradual Occlusion of Large Arteries with Polythene and Tantalum *Surgery 25* 184 1949

15 Crawford C and G Nylin Congenital Coarctation of the Aorta and Its Surgical Treatment *J Thoracic Surg 14* 347 1945

16 Cullen M L L G Steppacher B Greenspan H E Milliken Jr G W Moore and G C Morris Jr Studies on the Effects of Concomitant Venous Ligation in Acute Arterial Occlusion *Surg Gynec & Obst 89* 722 1949

17 Dandy W E Results Following Ligation of the Internal Carotid Artery *A M A Arch Surg 45* 521 1942

18 DeBakey M E Discussion of Paper by Child C G III R F Milnes G R Holswode and A L Gore Sudden and Complete Occlusion of the Portal Vein in the Macaca Mulatta Monkey *Ann Surg 132* 475 1950

19 ——— and F A Simeone Battle Injuries of the Arteries in World War II *Ann Surg 123* 534 1946

20 DeTakats G Anticoagulant Therapy in Surgery *J A M A 142* 527 1950

21 Deterling R A C C Coleman and M S Parshley Experimental Studies of the Frozen Homologous Aortic Graft *Surgery 29* 419 1951

22 Elkin D S Exposure of Blood Vessels *J A M A 132* 421 1946

23 Freeman N E F J Wylie and R S Gilfillan Regional Heparinization in Vascular Surgery *Surg Gynec & Obst 90* 406 1950

24 Gerbode F J Yee and F F Rundle Experimental Anastomoses of Vessels to the Heart Possible Application to Superior Venal Caval Obstruction *Surgery 25* 556 1949

25 Gius J A and D H Grier Venous Adaptation Following Bilateral Radical Neck Dissection with Excision of the Jugular Veins *Surgery 28* 305 1950

26 Grant J C B *Methods of Anatomy Descriptive and Deductive* 4th ed Baltimore Williams and Wilkins Company 1948

27 Grant J L W T Fitts and I S Ravdin Aneurysm of the Hepatic Artery *Surg Gynec & Obst 91* 527 1950

28 Greenberg M W Blood Supply of the Rectosigmoid and Rectum *Ann Surg 131* 100 1950

29 Grindley J H F C Mann and J L Bollman Effect of Occlusion of the Arterial Blood Supply to Normal Liver *A M A Arch Surg 62* 806 1951

30 Cross R F Complete Surgical Division of the Patent Ductus Arteriosus *Surg Gynec & Obst 78* 36 1944

31 ——— A H Bill Jr and E C Pierce Methods for Preservation and Transplantation of Arterial Grafts *Surg Gynec & Obst 88* 689 1949

32 ——— I S Hurwitt A H Bill and E C Pierce Preliminary Observations on the Use of Human Arterial Grafts in the Treatment of Certain Cardiovascular Defects *New England J Med 239* 578 1948

33 Halsted W S Ligations of the Left Subclavian Artery in Its First Portion *Johns Hopkins Hospital Reports 21* 19 1920 1924

34 Harman J W and R P Gwinn The Recovery of Skeletal Muscle Fibers from Acute Ischemia as Determined by Histologic and Chemical Methods *Am J Path 25* 741 1949

35 Henry A K *Extensile Exposure Applied to Limb Surgery* Edinburgh E & S Livingstone Ltd 1945

36 Hinman F Jr The Rational Use of Tourniquets *Internat Abstr Surg (Surg Gynec & Obst) 81* 357 1945

37 Holman E The Placement of Incisions in the Neck *Surg Gynec & Obst 78* 533 1944

38 ——— Problems in the Dynamics of Blood Flow I Conditions Controlling Collateral Circulation in the Presence of an Arteriovenous Fistula Following Ligation of an Artery *Surgery 26* 889 1949

39 Homans J Deep Quiet Venous Thrombosis in the Lower Limb Preferred Levels of Interruption of Veins Iliac Section or Ligation *Surg Gynec & Obst 79* 70 1944

40 Hufnagel C A Permanent Intubation of the Thoracic Aorta *A M A Arch Surg 54* 382 1947

41 ——— Preserved Homologous Arterial Transplants Forum on Fundamental Surgical Problems *Proceedings* Thirty Third Annual Clinical Congress of the American College of Surgeons September 1947 p 94

42 ——— Resection and Grafting of the Thoracic Aorta with Minimal Interruption of the Circulation *Proceedings* Thirty Fourth Annual Clinical Congress of the American College of Surgeons October 1948 *Forum on Fundamental Surgical Problems* p 69

43 Johnson J C K Kirby E F Greifenstein and A Castillo The Experimental and Clinical Use of Vein Grafts to Replace Defects of Large Arteries *Surgery 26* 945 1949

44 Keeffr E B C W DeW Andrus E Clenn G H Humphries II J W Lord W B Murphy and A S W Touroff The Blood Vessel Bank *J A M A 145* 888 1951

45 Kieslwetter W B and H B Shumaker Jr An Experimental Study of the Comparative Efficiency of Heparin and Dicumarol in the Prevention of Arterial and Venous Thrombosis *Surg Gynec & Obst 86* 687 1948

46 Ladd W E *Personal Communication*

47 Lazzari J H and F J Rack Method of Hemipelvectomy with Abdominal Exploration and Temporary Ligation of the Common Iliac Artery *Ann Surg 133* 267 1951

48 Lewis Sir Thomas *Vascular Disorders of the Limbs* London Macmillan and Co Ltd 1949

49 Linton R R Arteriosclerotic Popliteal Aneurysm *Surgery 26* 41 1949

50 Longmire W P Jr A Modification of the Roux Technique for Antethoracic Esophageal Reconstruction Anastomosis of Internal Mammary Artery and Mesenteric Blood Vessels *Surgery 22* 94 1947

51 MacDonald I Resection of the Axillary Vein in Radical Mastectomy Its Relation to the Mechanism of Lymphedema *Cancer 1* 618 1948

52 Makins G H *On Gunshot Injuries to*

the Blood Vessels New York William Wood and Co 1919

53 Markowitz J A Rappaport and A C Scott The Function of the Hepatic Artery in the Dog *Am J Digest Dis 16* 344 1949

54 Marrangoni A G and L P Cecchini The Preservation of Arterial Segments by the Freeze Drying Method Project NM 007 081 10 02 Naval Medical Research Institute National Naval Medical Center Bethesda Md

55 Martin H B DeValle H Ehrlich and W G Cahan Neck Dissection *Cancer 4* 441 1951

56 Matas R and C W Allen Conclusions Drawn from an Experimental Investigation into the Practicability of Reducing the Caliber of the Thoracic Aorta by a Method of Plication or Infolding of Its Walls by Means of a Lateral Parietal Suture Applied in One or More Stages *Ann Surg 58* 304 1913

57 Michels N A The Hepatic Cystic and Retroduodenal Arteries and Their Relations to the Biliary Ducts *Ann Surg 133* 503 1951 (April)

58 Miller R W P Harvey and C A Finch Antagonism of Dicumarol by Vitamin K Preparations *New England J Med 242* 211 1950

59 Miller H H A D Callow C S Welch and H E MacMahon The Fate of Arterial Grafts in Small Arteries *Surg Gynec & Obst 92* 581 1951

60 ——— and C S Welch Quantitative Studies on the Time Factor in Arterial Injuries *Ann Surg 130* 428 1949

61 Narath A Uber Enstehung der anamischen Lebernekrose nach Unterbindung der Arteria hepatica und ihre Verhutung durch arterio portale Anastomose *Deut Ztschr Chir 135* 305 1916

62 Nelson L E and A J Kremen Experimental Occlusion of Superior Mesenteric Vessels with Special Reference to the Role of Intravascular Thrombosis and its Prevention by Heparin *Surgery 28* 819 1950

63 Noer R J J W Derr and C G Johnston The Circulation of the Small Intestines An Evaluation of its Revascularizing Potential *Ann Surg 130* 608 1949

64 Owings J C and J F Hewitt Successful Experimental Ligation and Division of the Thoracic Aorta *Ann Surg 115* 596 1942

65 Parsons W B Discussion of Paper by Child C G III R F Milnes G R Holswade and A L Gore Sudden and Complete Occlusion of the Portal Vein in the Macaca Mulatta Monkey *Ann Surg 132* 475 1950

66 Pearse H F A Method for the Gradual Occlusion of the Aorta *Surg Gynec & Obst 46* 411 1928

67 ——— Experimental Studies on the Gradual Occlusion of Large Arteries *Ann Surg 112* 923 1940

68 Pemberton J DeJ and G R Livermore Surgical Treatment of Carotid Body Tumors Value of Anticoagulants in Carotid Ligation *Ann Surg 133* 837 1951

69 Pierce E C II R E Gross A H Bill and K Merrill Jr Tissue Culture Evaluation of the Viability of Blood Vessels Stored by Refrigeration *Ann Surg 129* 333 1949

70 ——— H F Rheinlander A R Moritz R E Gross and K Merrill Jr. Transplantation of Aortic Segments Fixed in 4 Per Cent Neutral Formalin *Am J Surg 78* 314 1949

71 Potts W J Technic of Resection of Coarctation of the Aorta with Aid of New Instruments *Ann Surg 131* 466 1950

72 ——— S Smith and S Gibson Anastomosis of the Aorta to a Pulmonary Artery Certain Types in Congenital Heart Disease *J A M A 132* 627 1946

73 Quiring D P *Collateral Circulation (Anatomical Aspects)* Philadelphia Lea and Febiger 1949

74 Reid M R Partial Occlusion of the Aorta with Silk Sutures and Complete Occlusion with Fascial Plugs The Effect of Ligatures on the Arterial Wall *J Exper Med 40* 293 1924

75 ——— Ligation of Large Arteries *Surg Gynec & Obst 58* 287 1934

76 Rienhoff W F Jr Ligation of the Hepatic and Splenic Arteries in the Treatment of Portal Hypertension with a Report of Six Cases Preliminary Report *Bull Johns Hopkins Hosp 88* 368 1951

77 Robinson L S The Collateral Circulation Following Ligation of the Inferior Vena Cava *Surgery 25* 329 1949

78 Rogers L Ligation of Common Carotid Artery Report of 19 Personal Cases *Lancet 1* 949 1949

79 Sako Y T C Chisholm K A Merendino and R L Varco An Experimental Evaluation of Certain Methods of Suturing the Thoracic Aorta *Ann Surg 130* 363 1949

80 Schilling J A F W McKee and W Wilt Experimental Hepatico Portal Arteriovenous Anastomoses *Surg Gynec & Obst 90* 473 1950

81 Silverstone B *Personal Communication* Presented at the 1951 Meeting of the Harvey Cushing Society April 1951 Hollywood Florida

82 Shumaker H B and R I Lowenberg Experimental Studies in Vascular Repair I Comparison of Reliability of Various Methods of End to End Arterial Suture *Surgery 24* 79 1948

83 Simeone F A H C Grillo and F Rundle On the Question of Ligation of the Concomitant Vein When A Major Artery Is Interrupted *Surgery 29* 932 1951

84 Smith S Studies in Experimental Vascular Surgery *Surgery 18* 627 1945

85 Sugarbaker E D and H M Wiley Simultaneous Tourniquet or Temporary Ligation of Both External Carotid Arteries for Resection of Malignant Lesions In and About the Mouth *Surgery 29* 296 1951

86 Swan H *Personal Communication*

87 ——— and F B Harper Ligation of Major Arteries *Surgery 28* 958 1950

88 ——— and H M Moretz Arterial Homografts III Use of Preserved Grafts in the Treatment of Neoplastic Disease Involving Peripheral Arteries *A M A Arch Surg 62* 767 1951

89 ——— H T Robertson and M E Johnson Arterial Homografts I The Fate of Preserved Aortic Grafts in the Dog *Surg Gynec & Obst 90* 568 1950

90 SWEET W H and H S BENNETT Changes in Internal Carotid Pressure During Carotid and Jugular Occlusion and Their Clinical Significance *J Neurosurg 5* 178 1948

91 ——— S J SARNOFF and L BAKAY A Clinical Method for Recording Internal Carotid Pressure *Surg Gynec & Obst 90* 327 1950

92 TANTURI C L I SWIGART and J F CANEPA Prevention of Death from Experimental Ligation of the Liver (Hepatic Proper) Branches of the Hepatic Artery *Surg Gynec & Obst 91* 680 1950

93 VEAL J R T J DUGAN W L JAMISON and R S BAUERSFELD Acute Massive Venous Occlusion of the Lower Extremities *Surgery 29* 355 1951

94 WARREN R War Wounds of Arteries *A M A Arch Surg 53* 86 1946

95 WATSON W L and S M SILVERSTONE Ligature of the Common Carotid Artery in Cancer of the Head and Neck *Ann Surg 109* 1 1939

96 WELCH C S A Technique for Portacaval Anastomosis (Eck Fistula) *Surg Gynec & Obst 85* 492 1947

97 ——— Medical Progress Portal Hypertension *New England J Med 243* 598 1950

98 ——— and A D CALLOW *Unpublished Data*

99 WISE R A Control of the Common Iliac Artery during Sacroiliac Disarticulation (Hemipelvectomy) *Ann Surg 128* 993 1948

100 YEAGER G H and R A COWLEY Studies on the Use of Polythene as a Fibrous Tissue Stimulant *Tr Am S A 66* 265 1948

101 YUDIN S S The Surgical Construction of 80 Cases of Artificial Esophagus *Surg Gynec & Obst 78* 561 1944

CHAPTER 13

1 GLASSER O E H QUIMBY L S TAYLOR and J L WEATHERWAX *Physical Foundations of Radiology* 2nd ed New York Paul B Hoeber Inc 1954

2 HAHN P F ed *Therapeutic Use of Artificial Radioisotopes* New York John Wiley & Sons Inc 1956

3 HINE G J and G L BROWNELL eds *Radiation Dosimetry* New York Academic Press Inc 1956

4 JOHNS H E *The Physics of Radiation Therapy* Springfield Ill Charles C Thomas 1953

5 MEREDITH W J ed *Radium Dosage* Baltimore The Williams & Wilkins Company 1947

6 MORGAN R H and K E CORRIGAN eds *Handbook of Radiology* Chicago The Year Book Publishers Inc

7 PATERSON R *The Treatment of Malignant Disease by Radium and X Rays* Baltimore The Williams & Wilkins Company 1953

8 POLLARD E and W L DAVIDSON *Applied Nuclear Physics* New York John Wiley and Sons Inc

9 WACHSMANN F and A DIMOTSIS *Kurven und Tabellen für die Strahlentherapie* Stuttgart S Hirzel Verlag 195[illegible]

10 WEYL C and S R WARREN Jr *Radiologic Physics* Springfield Ill Charles C Thomas 1951

11 WILSON C W *Radium Therapy* Baltimore The Williams & Wilkins Company 1956

CHAPTER 14

1 ANDERSON R S *Investigations into Differentiation and Other Morphological Changes in Malignant Tumours Following Therapeutic Irradiation with X Rays and Radium* Copenhagen Ejnar Munksgaard Forlag 1949

2 ARENSON A N Clinical Results and Histological Changes Following Radiation Treatment of Cancer of the Corpus Uteri *Am J Roentgenol 36* 461 1936

3 ARIEL I M *Personal communication*

4 ——— The Effect of Single Massive Doses of Roentgen Radiation upon the Liver *Radiology 57* 561 1951

5 BRUNSCHWIG A and E KANDEL Correlation of the Histological Changes and the Clinical Symptoms in Irradiated Hodgkin s Disease and Lymphoblastoma Lymph Nodes *Radiology 23* 315 1934

6 COGAN D G Lesions of the Eye from Radiant Energy *J A M A 142* 145 1950

7 DESJARDINS A U Classification of Tumors from the Standpoint of Radiosensitiveness *Am J Roentgenol 32* 493 1934

8 FITZPATRICK T B E C LERNER and W H SUMMERSON Mammalian Tyrosinase *A M A Arch Dermat & Syph 59* 620 1949

9 FOGG L C and S WARREN A Comparison of the Cytoplasmic Changes Induced in the Walker Rat Carcinoma 256 by Different Types and Dosages of Radiation *Am J Cancer 31* 567 1937

10 ——— and ——— Some Cytological Effects of Therapeutic Irradiation *Cancer Res 1* 649 1941

11 HEMPELMANN L H H LISCO and J G HOFFMANN The Acute Radiation Syndrome *Ann Int Med 36* 279 1952

12 HENSHAW P S and D S FRANCIS Consideration of Biological Factors Influencing Radiosensitivity of Cells *J Cell and Comp Physiol 7* 173 1935

13 JOLLES B and P C KOLLER The Role of Connective Tissue in the Radiation Reaction of Tumors *Brit J Cancer 4* 77 1950

14 KARSNER H T *Tumors of the Adrenal (Atlas of Tumor Pathology)* Washington D C Armed Forces Institute of Pathology 1950

15 LENZ M J WELLS and A P STOUT "Hodgkin s Disease and Lymphosarcoma" In U V PORTMANN *Clinical Radiation Therapy* New York Thomas Nelson & Sons 1950

16 MARKS H A New Approach to Roentgen Therapy of Cancer With the Use of a Grid *J Mt Sinai Hosp 17* 46 1950

17 MAXIMOW A Studies on the Changes Produced by Roentgen Rays in Inflamed Connective Tissue *J Exper Med 37* 319 1923

18 McCARTHY W D and G T PACK Malignant Blood Vessel Tumors *Surg Gynec & Obst 91* 464 1950

19 PACK G T *Personal communication*

20 SAPHIR O Fate of Carcinoma Emboli in the Lung *Am J Path* [illegible]

21 SCHREK R Dark Field Observations on Lymphocytes Exposed to X Rays and Other In

jurious Agents *Proc Soc Exper Biol & Med* *64* 381 1947

22 SHEEHAN J F H E SCHMITZ and J TOWNE Changes in the Uterus After Eradication of Endometrial Adenocarcinoma by Radiotherapy *A M A Arch Path* *39* 237 1945

23 STAFF OF BIOCHEMICAL RESEARCH FOUNDATION *Neutron Effects On Animals* Baltimore William & Wilkins Company 1947

24 STETSON C G and M D SCHULZ Carcinoma of the Eyelid Analysis of 301 Cases and Review of the Literature *New England J Med* *241* 725 1949

25 STEWART F and J H FARROW The Radiosensitivity of Tumors in G T PACK and E M LIVINGSTON eds *The Treatment of Cancer and Allied Diseases* New York Paul B Hoeber Inc 1940 vol 1 p 98

26 WARREN S *Address* delivered before the American Society of Pathologists and Bacteriologists New York 1952

27 ——— Effects of Radiation on Normal Tissues *A M A Arch Path* *34* 443 562 749 917 1070 1942 *35* 121 304 1943

28 ——— Pathologic Aspects of the Radiosensitivity of Malignant Tumors *Am J Roentgenol* *48* 384 1942

29 WOCHOWSKI T J and H CHENAULT Degenerative Effects of Large Doses of Roentgen Rays on the Human Brain *Radiology* *45* 227 1945

30 ZIRKLE E Relationships Between Chemical and Biological Effects of Ionizing Radiations *Radiology* *52* 846 1949

CHAPTER 15

1 BARRON E S G *et al* Studies on the Mechanism of Action of Ionizing Radiations I Inhibition of Enzymes by X Rays *J Gen Physiol* *32* 537 1949

2 BACQ Z M and P ALEXANDER *Fundamentals of Radiobiology* New York Academic Press Inc 1955

3 BEHRENS CHARLES F *Atomic Medicine* New York Thomas Nelson & Sons 1949

4 DOWDY A H L R BENNETT and S M CHASTAIN Summary of the Effects of Varying Oxygen Tension on the Response of Mammalian Tissue to Roentgen Irradiation *Report No 55* Atomic Energy Project University of California (Los Angeles) 1950

5 EVANS ROBLEY D Fundamentals of Radioactivity and Its Instrumentation in *Advances in Biological and Medical Physics* J H LAWRENCE and J G HAMILTON (eds) New York Academic Press Inc 1948 vol 1

6 GRAY L H Comparative Studies of the Biological Effects of X Rays Neutrons and Other Ionizing Radiations in *Applied Biophysics* N HOWARD JONES ed New York Chemical Publishing Co Inc 1949

7 GRAY L H A D CONGER M EBERT S HORNSEY and O C A SCOTT The Concentration of Oxygen Dissolved in Tissues at the Time of Irradiation as a Factor in Radiotherapy *Brit J Radiol* *26* 638 1953

8 HEMPELMANN L H H LISCO and J G HOFFMAN The Acute Radiation Syndrome A Study of Nine Cases and a Review of the Problem *Ann Int Med* *36*:279 1952

9 HOLLAENDER A (ed) *Radiation Biology* New York McGraw Hill Book Co Inc 1954 1955 Vol 1 *High Energy Radiation* vol 2 *Ultraviolet and Related Radiations*

10 LEA D E *Actions of Radiations on Living Cells* New York The Macmillan Co 1947

11 NICKSON J J (ed) *Symposium on Radiobiology The Basic Aspects of Radiation Effects on Living Systems* New York John Wiley and Sons Inc 1952

12 RUSSELL W L Radiation Induced Mutations in the Mouse *Oak Ridge Nat Lab Quar Prog Rep* November 10 1951

13 SPEAR F G The Biological Effects of Penetrating Radiations in *Applied Physics* N HOWARD-JONES (ed) New York Chemical Publishing Co Inc 1949

14 ——— (ed) Certain Aspects of the Action of Radiation on Living Cells *Brit J Radiol* Supplement No 1 London 1947

15 ——— *Radiations and Living Cells* New York John Wiley and Sons Inc 1953

16 TOBIAS C A H O ANGER and J H LAWRENCE Radiological Use of High Energy Deuterons and Alpha Particles *Amer J Roentgenol* *67* 1 1952

17 WARREN S Effects of Radiation on Normal Tissue Parts I XV *A M A Arch Pathol* *34* 443 562 749 917 1070 1942 *36* 121 304 1943

18 ——— Chairman *Report of the Committee on Pathologic Effects of Atomic Radiation* Publication 452 National Academy of Sciences National Research Council 1956

CHAPTER 16

1 BRAESTRUP C B and I H BLATZ Physical Factors of Low voltage Contact Roentgen Therapy *Radiology* *35* 198 1940

2 CHAOUL H and A ADAM Die Rontgennahbestrahlung maligner Tumoren *Strahlentherapie* *48* 31 1933

3 CHAMBERLAIN R H Recent Advances in Contact Therapy Equipment and Usage *Pennsylvania M J* *53* 359 1950

4 DAY F H and L S TAYLOR Absorption of X rays in Air *Radiology* *52* 239 1949

5 ——— Thimble Chamber Calibration on Soft Roentgen Rays *Am J Roentgenol* *61* 543 1949

6 FRANK A The Special Importance of Dosage Technique in Near Distance Roentgen Therapy *Fortschr Geb Rontgenstrahlen* *53* 206 1936

7 GOIN L S and E F HOFFMAN Use of Intravesical Low Voltage Contact Roentgen Irradiation in Cancer of the Bladder *Radiology* *37* 545 1941

8 ——— Low Voltage Contact Irradiation Further Experience *Radiology* *42* 241 1944

9 HENDTLASS R F Low Voltage X ray Therapy with a Beryllium Window Tube Part III *Brit J Radiol* *24* 134 1951

10 HOWES W E and M R CAMIEL Contact Roentgen Therapy *Amer J Roentgenol* *48* 360 1942

11 JENNINGS W A Physical Aspects of the Roentgen Radiation from a Beryllium Window Tube *Acta radiol* *33* 435 1950

12 ——— Low Voltage X ray Therapy with

a Beryllium Window Tube Part II *Brit J Radiol 24* 134 1951

13 KEPP R K and F WACHSMANN Gemeinsames und Unterschiede der Chaoulschen Nahbestrahlung und der Gottinger gynakologischen Bestrahlungsmethode *Strahlentherapie 81* 287 1950

14 LAMARQUE P and C GROS Radiotherapie de contact de cancer du rectum *Bull de cancer 33* 76 1946

15 LUTTERBECK E F and I F HUMMON Uniform Contact Roentgen Therapy for Large Areas *Radiology 56* 108 1951

16 MAYNEORD W V Measurements of Low Voltage X rays *Brit J Radiol 9* 215 1936

17 PENDERGRASS E P P J HODES and C J GARRAHAN Roentgen Therapy by the Method of Chaoul *Radiology 32* 142 1939

18 ——— and R H CHAMBERLAIN Contact Roentgen Therapy *in Clinical Therapeutic Radiology* New York Thomas Nelson and Sons 1950

19 QUIMBY E H and E F FOCHT Dosage Measurements in Contact Roentgen Therapy *Am J Roentgenol 50* 653 1943

20 ROGERS T H High Intensity Radiation from Beryllium Window X ray Tubes *Radiology 48* 594 1947

21 SMITHERS D W *The Treatment of Accessible Cancer* Baltimore Williams & Wilkins Company 1946

CHAPTER 17

1 ACKERMAN L V and J A DEL REGATO *Cancer Diagnosis Treatment and Prognosis* St Louis C V Mosby Co 1947 *a* p 77 *b* p 281 *c* p 432 *d* p 774

2 AHLBOM H E Mucous and salivary gland tumours *Acta radiol Supp 23* 1 1935

3 ——— Malignant Tumors of Testis Treatment at Radiumhemmet Stockholm *Acta radiol 28* 669 1947

4 ALLAN M S and A T HERTIG Carcinoma of Ovary *Am J Obst & Gynec 58* 640 1949

5 BACHMAN A L and W HARRIS Roentgen Therapy for Pituitary Adenoma Correlation of Tumor Dose With Response in 64 Cases *Radiology 53* 331 1949

6 BACLESSE F Resultats eloignes du traitement roentgentherapique des epitheliomas glosso epiglottiques (base linguale vallecules epiglotte) *J radiol et electrol 25* 190 1942 1943

7 ——— and G DULAC Les tumeurs malignes du rhinopharynx *Bull Assoc franç etude cancer 31* 160 1943

8 BERVEN E G E Malignant Tumors of the Tonsil a Clinical Study With Special Reference to Radiological Treatment *Acta radiol Supp 11* 1 1931

9 BLADY J V Treatment of Recurrences and Evaluation of Criteria for Selection of Treatment of Cancer of Larynx *Am J Roentgenol 58* 331 1947

10 BUSCHKE F Radiotherapy of Pituitary Adenomas *West J Surg 58* 271 1950

11 CADE S Treatment and Results in Cancer of the Breast *Am J Roentgenol 62* 326 1949

12 COHEN O H and W I PALAZZO The Grid Technique of Radiotherapy With Depth Dose Measurements *Am J Roentgenol 67* 470 1952

13 COLEY B L N L HIGINBOTHAM and L BOWDEN Endothelioma of Bone (Ewing s Sarcoma) *Ann Surg 128* 533 1948

14 COUTARD H Roentgen Therapy of Epitheliomas of the Tonsillar Region Hypopharynx and Larynx From 1920 to 1926 *Am J Roentgenol 28* 313 1932

15 ——— Roentgen Therapy of Epitheliomas of the Upper Air Passages *Laryngoscope 46* 407 1936

16 ——— Present Conception of the Treatment of Cancer of the Larynx *Radiology 34* 136 1940

17 DEL REGATO J A Roentgen Therapy of Lymphosarcomas of the Tonsil *Radiation Therapy* Seattle Tumor Inst (No 2) 67 1941

18 DESJARDINS A U F FIGI and L M VAUGHN Roentgen Treatment for Extensive Epithelioma of Larynx Results in 139 Cases *Am J Roentgenol 60* 29 1948

19 EDWARDS A T Carcinoma of the Bronchus *Thorax 1* 1 1946

20 ELLIS F Radiotherapy in Treatment of Pituitary Basophilism and Eosinophilism *Proc Roy Soc Med 42* 853 1949

21 ENGELSTAD R B Carcinoma of Esophagus Cured with Radiotherapy *Year Book of Radiology* Chicago Year Book Publishers Inc 1949 p 403

22 EVANS W G and G PICCIOTTO Chromophobe Adenoma of Pituitary Evaluation of Its Treatment and Some Case Reports *Brit J Radiol 21* 330 1948

23 FREED J H and E P PENDERGRASS Diagnosis and Treatment of Primary Ovarian Carcinoma With Special Reference to Radiation Therapy *Cancer Res 8* 361 1948

24 GEIST R M and U V PORTMANN Primary Malignant Tumors of the Nasopharynx *Am J Roentgenol 68* 262 1952

25 GLASSER O E H QUIMBY L S TAYLOR and J L WEATHERWAX *Physical Foundations of Radiology* New York Paul B Hoeber Inc 1944

26 GODTFREDSEN E Ophthalmologic and Neurologic Symptoms of Malignant Nasopharyngeal Tumours *Acta psychiat et neurol scandinav Supp 34* 1 1944

27 GRAHAM J M The Surgery of the Hypopharynx Post Cricoid Carcinoma *Edinburgh M J 49* 164 1942

28 ——— and R MCWHIRTER Carcinoma of the Thyroid *Proc Roy Soc Med 40* 669 1948

29 GROSS R E and E B D NEUHAUSER Treatment of Mixed Tumors of Kidney in Childhood *Pediatrics 6* 843 1950

30 GUZMAN L Cancer of the Thyroid *Radiology 51* 820 1948

31 HAAGENSEN C D Treatment and Results in Cancer of the Breast at Presbyterian Hospital New York *Am J Roentgenol 62* 328 1949

32 HARE H F W C MULRY and C F SORNBERGER Lymphoid Tumors *Radiology 50* 506 1948

33 ——— and F A SALZMAN Cancer of Thyroid 10 20 Year Follow up *Am J Roentgenol 63* 881 1950

34 HARNETT W L Statistical Report on 955 Cases of Cancer of the Cervix Uteri and 321 Cases of Cancer of Corpus Uteri *Brit J Cancer 3* 433 1949

35 HARRIS W Recent Clinical Experience With the Grid in the X Ray Treatment of Advanced Cancer *Radiology 58* 343 1952

36 ——— R KRAMER and S M SILVERSTONE Radiation Therapy for Cancer of the Larynx *in* U V PORTMANN *Clinical Therapeutic Radiology* New York, Thomas Nelson & Sons *1950* p *136*

37 HINTZE A *In* L V ACKERMAN and J A DEL REGATO *Cancer Diagnosis Treatment and Prognosis* St Louis C V Mosby Co 1947 p 643

38 HUNT H B Response of Carcinoma of Cervix Uteri to Fractionated Radium and Roentgen Therapy Given Concurrently *Am J Roentgenol 64* 446 1950

39 INGRAHAM F D O T BAILEY and W F BARKER Medulloblastoma Cerebelli Diagnosis Treatment and Survivals With Report of 56 Cases *New England J Med 238* 171 1948

40 JACKSON C L Laryngofissure for Cancer of the Larynx *A.M A Arch Otolaryng 33* 520 1941

41 JACOBSON L E and A LIPMAN Depth Dose Investigation for Perforated Grid Therapy at 200 Kilovolts *Am J Roentgenol 67* 458 1952

42 JACOBSSON F Carcinoma of Hypopharynx Clinical Study of 322 Cases Treated at Radiumhemmet 1939 47 *Acta radiol 34* 1 1951

43 JACOX H W and G F CAHILL Treatment of Diseases of the Kidneys and Adrenal Glands" *in U V* PORTMANN *Clinical Therapeutic Radiology* New York Thomas Nelson & Sons *1950* p *254*

44 JOLLES B Radiotherapy of Accessible Malignant Tumors by Alternating Chess Board Method *Lancet* 2 603 1949

45 KERR D H Irradiation of Pituitary Tumors Results in 50 Cases *Am J Roentgenol 60* 348 1948

46 ——— and H B ELKINS Carcinoma of the Ovary *Am J Roentgenol 66* 184 1951

47 KOHLER A Zur Rontgentiefentherapie Mit Massendosen *Munchen Med Wchnschr 56* 2314 *1909*

48 KOHLER R Roentgen Treatment of Cancer of Esophagus *Acta radiol 35* 207 1951

49 LEDDY E T Treatment of Intrathoracic Diseases *in* U V PORTMANN *Clinical Therapeutic Radiology* New York Thomas Nelson & Sons 1950 p 179

50 LENZ M Causes of Failure of Roentgen Therapy in Cancer of the Larynx *Am J Roentgenol 46* 21 1941

51 ——— Roentgen Therapy of Primary Cancer of the Nasopharynx *Am J Roentgenol 48* 816 1942

52 ——— Radiocurability of cancer *Am J Roentgenol 67* 428 1952

53 LEUCUTIA T W A EVANS JR and J C COOK Radiation Therapy of Malignant Tumors of Testis Long Range Statistical Analysis With Review of Literature *Radiology 51* 177 1948

54 LIBERSON F Value of Multiperforated Screen in Deep X Ray Therapy *Radiology 20* 186 1933

55 LOEVINGER R Depth Dose Curves for Grids in X Ray Therapy *Radiology 58* 351 1952

56 MARKS H Clinical Experience With Irradiation Through a Grid *Radiology 58* 338 1952

57 MARTIN H E and E L SUGARBAKER Cancer of the Tonsil *Am J Surg 52* 158 1941

58 MCWHIRTER R Value of Simple Mastectomy and Radiotherapy in Treatment of Cancer of Breast *Brit J Radiol 21* 599 1948

59 ——— and N DOTT Discussion of Classification of Brain Tumors and Radiosensitivity" *in* R PATERSON *The Treatment of Malignant Disease by Radium and X rays* London Edward Arnold & Co 1948

60 MILLEN J L E Carcinoma of Bladder III Treatment by Radon Seed Implantation and Deep X Ray Therapy *Brit J Radiol 22* 407 1949

61 MILLER N F and C W HENDERSEN Corpus Carcinoma Study of 322 Cases *Am J Obst & Gynec 52* 894 1946

62 NESBIT R M and F M ADAMS Wilms Tumor Review of 16 Cases *J Pediat 29* 295 1946

63 NIELSEN J Roentgen Treatment of Malignant Tumors of the Nasopharynx *Acta radiol 26* 133 1945

64 ——— and Sv H JENSEN Rotation Therapy Its Basis and Possibilities *Acta radiol 23* 51 1942

65 NOHRMAN B A Treatment of Cancer of Breast by X Rays and Halsted s Operation *J radiol et électrol 29* 403 1948

66 O CONNELL H V and C F GESCHICKTER Tumors of Testes Five Year Follow up Study *U.S Armed Forces M J 1* 719 1950

67 PACK G T and E M LIVINGSTON Editors Introduction Treatment of Cancer of the Breast" *in Treatment of Cancer and Allied Diseases* 1st ed New York Paul B Hoeber Inc 1940

68 PATERSON R *Treatment of Malignant Disease by Radium and X rays* London Edward Arnold & Co 1948

69 PORTMANN U V Treatment of Diseases of the Breast *in* U V PORTMANN *Clinical Therapeutic Radiology* New York Thomas Nelson & Sons 1950 ch 16 p 208

70 REESE A B G R MERRIAM JR and H E MARTIN Treatment of Bilateral Retinoblastoma by Irradiation and Surgery *Am J Ophth 32* 175 1949

71 SHIMKIN M B Duration of Life in Untreated Cancer *Cancer 4* 1 1951

72 SOSMAN M C Technic of X Ray Therapy of Brain Tumors *in* C G DYKE and L M DAVIDOFF *Roentgen Treatment of Diseases of the Nervous System* Philadelphia Lea & Febiger 1942 p 32

73 STONE H W and H VERMUND Role of X Ray Therapy in Carcinoma of the Breast *Journal Lancet 70* 247 1950

74 TAYLOR G W Treatment and Results in Cancer of Breast *Am J Roentgenol 62* 341 1949

75 WELLS D B Audit of Treatment of Breast Cancer at Hartford Hospital 1932 39 *Connecticut M J 14* 3 1950

76 WINDEYER B W Cancer of Breast *Am J Roentgenol 62* 345 1949

CHAPTER 18

1 Buschke F S T Cantril and H M Parker *Supervoltage Roentgen Therapy* Springfield Ill Charles C Thomas 1950

2 Cade Sir Stanford *Malignant Disease and Its Treatment by Radium* 2nd ed Bristol John Wright & Sons Ltd 1949 vol 2 p 341

3 Dresser R Further Observations on the Use of Three Million Volt Roentgen Therapy *Radiology 50* 645 1948

4 Friedman M (See Vol VI Chapter 18)

5 Glasser O E H Quimby L S Taylor and J L Weatherwax *Physical Foundations of Radiology* 2nd ed New York Paul B Hoeber Inc 1952

6 Gray L H Certain Aspects of the Action of Radiation on Living Cells *Brit J Radiol Supp No 1* 1947 p 13

7 Holmes G W and M D Schulz Supervoltage Radiation Review of the Cases Treated During an Eight Year Period (1937 1944) *Am J Roentgenol 55* 533 1946

8 Jones A Clinical Reactions and Injuries in Supervoltage Therapy *Proc Roy Soc Med 41* 703 1948

9 Lea D E Certain Aspects of the Action of Radiation on Living Cells *Brit J Radiol Supp No 1* 1947 p 39

10 Lederman M Quoted by Cade [2] loc cit p 328

11 Mayneord W V Some Applications of Nuclear Physics to Medicine *Brit J Radiol Supp No 2* 1950 p 16

12 Mudd S G "Clinical Application of Super Hard X Rays in the Treatment of Cancer" in G T Pack and E M Livingston (eds) *Treatment of Cancer and Allied Diseases* 1st ed New York Paul B Hoeber Inc 1940 vol 1

13 Nielsen J Clinical Results with Rotation Therapy in Cancer of the Esophagus *Acta radiol 26* 361 1945

14 Phillips R Treatment of Inoperable Carcinoma of the Rectum *Proc Roy Soc Med 35* 768 1942

15 ——— *Supervoltage X Ray Therapy* London H K Lewis & Co Ltd 1944

16 ——— The Indications for the Use of Supervoltage Irradiation *M Ann District* [illegible] 4 535 1955

17 ——— Principles and Results of Palliative Radiotherapy in Nonresectable Cancer *M Clin North America 40* 807 1956

18 ——— D A Karnofsky L D Hamilton and J J Nickson Roentgen Therapy of Hepatic Metastases *Am J Roentgenol 71* 826 1954

19 Spiers F W Effective Atomic Number and Energy Absorption in Tissues *Brit J Radiol* [illegible] 1946

20 ——— The Influence of Energy Absorption and Electron Range on Dosage in Irradiated [illegible] *Brit J* [illegible] 1949

21 Stenstrom K W and K I Marvin [illegible] Measurements With Bone Chambers [illegible] Rotation Therapy [illegible] *Am J Roentgenol* [illegible] 1946

22 Trump J G Physical Basis for the High [illegible] of Supervoltage Roentgen Rays [illegible] 1948

23 Watson W L and J Urban Million Volt Roentgen Therapy for Intrathoracic Cancer *Am J Roentgenol 49* 299 1943

24 Williams I G Million volt X Ray Therapy *Proc Roy Soc Med 41* 709 1948

25 ——— Carcinoma of the Rectum and Anal Canal Treatment With Very High Voltage X Ray Therapy *Brit J Surg 36* 376 1949

26 ——— The Treatment of Advanced Cancer of the Rectum *Proc Roy Soc Med 43* 1083 1950

27 Wood C A P and J W Boag Researches on the Radiotherapy of Oral Cancer *London Med Research Council Sp Rep No 267* 1950

28 Zuppinger A "Radiation Therapy of Malignant Tumors of the Prostate" in G T Pack and E M Livingston eds *Treatment of Cancer and Allied Diseases* 1st ed New York Paul B Hoeber Inc 1940 vol 3

CHAPTER 19

1 Archangelsky B Über ein neues Prinzip in der Technik der Tiefentherapie und die dazu nötige Apparatur *Fortschr Geb Röntgenstrahlen 39* 1129 1929

2 Bischoff K Der Konvergenzstrahler eine Röntgenstrahlenquelle mit extrem hohen prozentualen Tiefendosen *Strahlentherapie 81* 365 1950

3 Dessauer F and G Mutheresm Die Rotationsbestrahlung *Fortschr Geb Röntgenstrahlen 56* 218 1937

4 Dessauer F K Lion and G Mutheresm Versuche mit der Rotationsbestrahlung *Strahlentherapie 60* 546 1937

5 Flax N A Deep Therapy Table with a Tube Stand Combined and Revolving in Arc about the Table Intensity Distribution within Paraffin Pelvis for Various Portals of Entry *Radiology 28* 477 1937

6 Green A W A Jennings and F Bush Rotational Roentgen Therapy in the Horizontal Plane *Acta radiol 31* 273 1949

7 Hawley S J A Method of Obtaining Greater Ratio of Deep to Surface Dosage *Am J Roentgenol 42* 760 1939

8 ——— Rotation Therapy *Radiology 35* 65 1940

9 ——— Rotation Therapy Theory and Clinical Applications *Radiology 51* 205 1948

10 Henschke U Über Rotationsbestrahlung *Fortschr Geb Röntgenstrahlen 58* 456 1938

11 Jensen W Hoffer J Nielsen and A Thomsen Evaluation of Different Factors in Rotation Therapy *Acta radiol* [illegible] 1944

12 Knox R and A St G Caulfield A New Therapeutic X ray Localizer *Brit J Radiol* [illegible] 1915

13 Kohl M D R P 19[illegible] 1906

14 Kohler A Die Pendelbestrahlung ein Hilfsmittel in der Behandlung inoperabler tief gelegener Krebse des Verdauungstraktus [illegible] 1919

15 [illegible] Kleine Erfahrungen mit der Pendelbestrahlung [illegible] *Strahlentherapie 81* 315 1950

16 [illegible] J S R A Harvey [illegible] J W Beattie [illegible]

pects of Rotation Therapy with the Betatron (I) *Am J Roentgenol 65* 947 1951
17 MEYER H Das Problem der Kreuz feuerwirkung in der gynäkologischen Röntgen therapie *Zentralbl Gynak 48* 1741 1913
18 MUNSON R J X ray Therapy with a Con tinuously Rotating Beam Part I Apparatus and Associated Physical Problems *Brit J Radiol 19* 405 1946
19 NAKAIDZUMI M and T MIYAKAWA Über die räumliche Dosisverteilung der Röntgenstrah len bei der Rotationsbestrahlung *Strahlenthera pie 66* 538 1939
20 ——— and ——— Zur Rotationsbes trahlung mit Hilfe einer ständigen Durchleuch tungskontrolle fur den Osophaguskrebs *Strah lentherapie 68* 254 1940
21 NEUMANN W and F WACHSMANN Er mittlung der Herddosis bei Rotationsbestrahlung unter Berucksichtigung der Absorptionsunter schiede in Gewebe *Strahlentherapie 71* 438 1942
22 ——— and ——— Klinische Erfahrun gen bei Rotationsbestrahlung *Strahlentherapie 75* 323 1944
23 NIELSEN H *Rotationsbestraaling* Copen hagen Ejnar Munksgaard Forlag 1951 pp 1 163 (Dissertation)
24 NIELSEN J and SV HOFFER JENSEN Some Experimental and Clinical Lights on the Rotation Therapy its Basis and Possibilities *Acta radiol 23* 51 1942
25 ——— Clinical Results with Rotation Therapy in Cancer of the Esophagus *Acta ra diol 26* 361 1945
26 POHL E D R P 296657 1913
27 ROCHEMONT R DU MESNIL DE Die Dosi erungsgrundlagen der Rotationsbestrahlung *Strahlentherapie 60* 648 1937
28 ——— Die Stellung der Bestrahlungsver fahren mit wanderndem Strahlenkegel im Rah men der modernen Entwicklung der strahlen therapeutischen Methodik *Strahlentherapie 71* 512 1942
29 ——— *Die Strahlentherapie* Stuttgart Thieme Verlag 1949 p 323
30 STEED P R *et al* Symposium on Small Field X ray Therapy for Deep Seated Tumors with Special Reference to Rotation Technique *Brit J Radiol* 22 185 1949
31 TRUMP J G E W WEBSTER K A WRIGHT W W EVANS R C GRANKE H F HARE S W LIPPINCOTT JR and D SAWYER Physical and Clinical Aspects of Supervoltage Rotational Therapy *Radiology 57* 157 1951

CHAPTER 20

1 CHASE H B H QUASTLER and L S SKAGGS Biological Evaluation of 20 Million Volt Roentgen Rays II Decoloration of Hair in Mice *Am J Roentgenol 57* 359 1947
2 HAAS L R A HARVEY and J S LAUGH LIN Biological Evaluation of Skin Effects of the 23 Mev Betatron *Am J Roentgenol 68* 644 1952
3 HARVEY R A L HAAS and J S LAUGHLIN Preliminary Clinical Experience with the Beta tron *Radiology 56* 394 1951
4 ——— ——— and ——— Betatron Can cer Therapy *Radiology 58* 23 1952
5 JOHNS H E The Betatron in Cancer Ther apy *Nucleonics 7* 76 1950
6 KERST D W The Acceleration of Electrons by Magnetic Induction *Phys Rev 60* 47 1941
7 ——— The Betatron *Radiology 40* 115 1943
8 LAUGHLIN J S R A HARVEY L L HAAS J E LINDSAY and J W BEATTIE Physical As pects of Rotation Therapy with the Betatron I *Am J Roentgenol 65* 947 1951
9 ——— and W D DAVIES Procedure in Dose Distribution Measurement of 25 Mev X Rays *Science 3* 514 1950
10 ——— J W BEATTIE J E LINDSAY and R A HARVEY Dose Distribution Measurements with the Illinois Medical Betatron *Am J Roent genol 65* 787 1951
11 ——— Considerations in the use of a 23 Mev Medical Betatron *Nucleonics 8* 5 (April) 1951
12 LUCE W M H QUASTLER and L S SKAGGS Biological Evaluation of 20 Million Volt Roentgen Rays III Recessive Sex Linked Lethals in Drosophila melanogaster *Am J Roent genol 62* 555 1949
13 QUASTLER H Studies on Roentgen Death in Mice I Survival Time and Dosage *Am J Roentgenol 54* 449 1945
14 ——— and R K CLARK Biological Eval uation of 20 Million Volt Roentgen Rays I Acute Roentgen Death in Mice *Am J Roent genol 54* 723 1945
15 ——— and E F LANZL Biological Eval uation of 20 Million Volt Roentgen Rays IV Efficiency and Dosage Range *Am J Roentgenol 63* 566 1950
16 ——— *et al* Techniques for Application of the Betatron to Medical Therapy *Am J Roentgenol 61* 591 1949
17 QUIMBY E H O GLASSER L S TAYLOR and J L WEATHERWAX *Physical Foundations of Radiology* New York Paul B Hoeber Inc 1949 p 402
18 SKAGGS L S J S LAUGHLIN and L H LANZL Technique of Producing an External Beam of Electrons from the Betatron *Phys Rev 73* 1223 1948
19 ——— G M ALMY D W KERST and L H LANZL Removal of the Electron Beam from the Betatron *Phys Rev 70* 95 1946
20 SPIERS F W Effective Atomic Number and Energy Absorption in Tissues *Brit J Ra diol 19* 52 1946

CHAPTER 21

1 AHLBOM H Points Regarding the Time Factor in Roentgen Irradiation with Divided Doses *Acta radiol 27* 223 1946
2 BARRINGER B S Twenty five Years of Radon Treatment of Cancer of the Bladder *J A M A 135* 616 1947
3 GIBSON J M W Treatment of Cancer of the Bladder *Brit J Urol 22* 424 1950
4 HAM H J British Empire Cancer Cam paign *13th Annual Report* pp 134 1936
5 HUNNINGS G Plastics and Radiotherapy *Plastics 15* 272 London 1950
6 MCWHIRTER R British Empire Cancer Campaign *12th Annual Report* 1935 p 131
7 MELVILLE G The Double Radium Mould

Radioactive Phosphorus *Internat Clin 3* 33 58 1939

16 Lawrence J H R Lowry B V Low Beer, and B Brown Chronic Myelogenous Leukemia A Study of 129 Cases in which Treatment was with Radioactive Phosphorus *J A M A 136* 672 677 1948

17 Marinelli L D Dosage Determination with Radioactive Isotopes *Am J Roentgenol 47* 210 216 1942

18 McConahey W M F R Keating and M H Power The Behavior of Radioiodine in the Blood *J Clin Invest 28* 191 198 1949

19 Rasmussen T B P V Harper E Yuhl and D M Bergenstal The Destruction of the Pituitary Gland in Metastatic Cancer with Yttrium 90 Pellets *Argonne Cancer Research Hospital Semiannual Report to the Atomic Energy Commission* pp 1 16 March 1955

20 Reinhard E H C V Moore C S Bierbaum and S Moore Radioactive Phosphorus as a Therapeutic Agent A Review of the Literature and Analysis of the Results of Treatment of 155 Patients with Various Blood Dyscrasias Lymphomas and Other Malignant Neoplastic Diseases *J Lab & Clin Med 31* 107 218 1946

21 Sherman A I M Bonebrake and W M Allen The Application of Radioactive Colloidal Gold in the Treatment of Pelvic Cancer *Am J Roentgenol 66* 624 628 1951

22 Stanley M M and E B Astwood Accumulation of Radioactive Iodide by Thyroid Gland in Normal and Thyrotoxic Subjects and Effect of Thiocyanate on its Discharge *Endocrinology 42* 107 123 1948

23 Thygesen J C A Videboeck and I Villaume Treatment of Leukemia with Radioactive Sodium *Acta radiol 25* 305 316 1944

CHAPTER 26A

1 Colmery B H Jr Preparation of Seeds of Radioactive Gold 198 and Their Use in Cancer Therapy *M Sc Thesis* The Ohio State University 1951

2 Henschke U K Interstitial Implantation with Radioisotopes " in *Therapeutic Use of Artificial Radioisotopes* P F Hahn (ed) New York John Wiley & Sons Inc 1956

3 ——— A G James and W G Myers Radiogold Seeds in Clinical Radiation Therapy *Radiology 63* 390 1954

4 ——— ——— and ——— Radiogold Seeds for Cancer Therapy *Nucleonics 11* 46 1953

James A G U Henschke and W G … The Clinical … of Radioactive Gold Seeds (… 034 1953

R D \ … and J L Morton … Radioa … lt in Non resectable … C … cer 4 1333 1951

——— Radioactive … Ad … r Surgery *Surg*

… of Radio … Malignanci … sity 195 … allendi … Coba

Plastic Tubing for Interstitial Radiation Therapy *Radiology 506* 553 1951

10 Myers W G Applications of Artificial Radioisotopes in Interstitial Radiation Therapy *Proceedings of 2nd National Cancer Conference* Vol 2 p 1652 New York American Cancer Society Inc 1952

11 ——— B H Colmery Jr and W M McLellon Radioactive Gold 198 for Gamma Radiation Therapy *Am J Roentgenol 70* 258 1953

12 ——— and ——— Radioactive Au 198 in Gold Seeds for Cancer Therapy *Cancer Res 12* 285 1952

13 Sinclair W K Artificial Radioactive Sources for Interstitial Therapy *Brit J Radiol 25* 417 1952

CHAPTER 26B

1 Greenberg Joseph H C Dudley and S S Sarkisian A Study of Methods for Interstitial Implantation of Radioactive Material II Filaments Containing Yttrium 90 *Am J Roentgenol 77* 852 1957

CHAPTER 27

1 Barnes A C J L Morton and G W Callendine The Use of Radioactive Cobalt in the Treatment of Carcinoma of the Cervix *Am J Obst & Gynec 60* 1112 1950

2 Callendine G W J L Morton and W G Myers Physical Considerations in Applying Cobalt[60] to Cancer Therapy *Nucleonics 7* 63 1950

3 Deutsch M L G Elliott and A Roberts Disintegration Schemes of Radioactive Substances VIII Cobalt *Physics Review 68* 193 1945

4 James A G R G Williams and J L Morton Radioactive Cobalt in Head and Neck in Inoperable Head and Neck Surgery Read Before the James Ewing Society at Memorial Hospital New York March 17 1951

5 ——— ——— and ——— Radioactive Cobalt as an Adjunct to Cancer Surgery *Surgery 30* 95 1951

6 ——— ——— and ——— The Use of Radioactive Cobalt in Non Resectable Head and Neck Cancer *Cancer 4* 1333 1951

7 Livingood J H and G T Seaborg Radioactive Isotopes of Cobalt *Physics Review 60* 913 1941

8 Maynford W V and A J Cipriani Some Applications of Nuclear Physics to Medicine *Brit J Research* (Supp 2) 1950

9 ——— and ——— Absorption of Gamma Rays from Cobalt[60] *Canad J Research (Supp 2) 25* 303 1947

10 Meschan I G Regnier J W Nelson and A W Lafferty Dosage Tables for Cobalt for Use with Interstitial Plaque and Intracavitary Applications *Am J Roentgenol 71* 3_0 1954

11 ——— R R Edwards and P J Rosen … Practical Physical Aspects in Use of Radioactive Cobalt[60] as Radium Substitute *Am J Roentgenol 65* 255 1951

12 ——— A Nettleship and I S Kerekes Comparative Skin Effects of "Identical"

Iodine in a Metastasis From Thyroid Carcinoma *Science* 95 362 1942

22 KOTTMEIER H L and G MOBERGER Experience with Radioactive Colloidal Gold as an Additional Treatment in the Radiotherapy of Uterine Cancer *Acta obst et gynec scandinav* 43 1 1955

23 LAWRENCE J H K G SCOTT and L W TUTTLE Studies on Leukemia With Aid of Radioactive Phosphorus *New International Clinics* 3 33 1939

24 LEDERMAN M and W K SINCLAIR Radioactive Isotopes for Beta and Gamma Ray Applicators *in Therapeutic Use of Artificial Radioisotopes* New York John Wiley & Sons Inc 1956

25 LOW BEER B V A External Therapeutic Use of Radioactive Phosphorus I Erythema Studies *Radiology* 47 213 1946

26 MATUSKA R A P F HAHN R I CARLSON S H AUERBACH and G R MENEELY The Lymphatic Drainage of Silver Coated Radioactive Gold Colloid Following Intrathoracic Administration to Pneumonectomized Dogs *J Thoracic Surg* 30 525 1955

27 MAYNEORD W V and W K SINCLAIR The Dosimetry of Artificial Radioactive Isotopes *in Advances in Biological & Medical Physics* New York Academic Press 1953 vol 3

28 MCCLURE C C JR E L CAROTHERS and P F HAHN Distribution and Pathology Resulting from the Intracerebral and Intraventricular Injection of Radioactive Gold and Silver Coated Radiogold Colloids *Am J Roentgenol* 73 81 1955

29 MORTON J L A C BARNES G W CALLENDINE and W G MYERS Individualized Interstitial Irradiation of Cancer of the Uterine Cervix Using Cobalt^{60} in Needles Inserted Through a Lucite Template *Am J Roentgenol* 65 737 1951

30 MULLER J H Intraperitoneal Application of Radioactive Colloids *in Therapeutic Use of Artificial Radioisotopes* New York John Wiley & Sons Inc 1956

31 MYERS W G and B H COLMERY, JR Radioactive Au^{198} In Gold Seeds For Cancer Therapy *Cancer Res* 12 285 1952

32 OSGOOD E E Treatment of Leukemias and Polycythemia Vera With Radioactive Phosphorus *in Therapeutic Use of Artificial Radioisotopes* New York John Wiley & Sons Inc, 1956

33 POCHIN E E "Radioiodine Treatment of Thyroid Carcinoma" *in Therapeutic Use of Artificial Radioisotopes* New York John Wiley & Sons Inc 1956

34 RAWSON R W and J B TRUNNELL Radioactive Iodine in the Study and Treatment of Carcinoma of the Thyroid *in A Manual of Artificial Radioisotope Therapy* New York Academic Press 1951

35 SEIDLIN S. M L D MARINELLI and ELEANOR OSHRY Radioactive Iodine Therapy—Effect on Functioning Metastases of Adenocarcinoma of the Thyroid *J A M A* 132 838 1946

36 SHELLY HARRY G R MENEELY and P F HAHN *In preparation*

37 SHERMAN A I Carcinoma of the Cervix Treated with Radioactive Gold Colloids *in Therapeutic Use of Artificial Radioisotopes* New York John Wiley & Sons Inc 1956

38 SINCLAIR W K Artificial Radioactive Sources for Interstitial Therapy *Brit J Radiol* 25 417 1952

39 SMITHERS D W D M WALLACE and N G TROTT The Use of Radioactive Isotopes in the Treatment of Patients with Bladder Tumors *in Therapeutic Use of Artificial Radioisotopes* New York John Wiley & Sons Inc 1956

CHAPTER 25

1 ANDREWS G A M BRUCER and E B ANDERSON *Radioisotopes in Medicine* United States Atomic Energy Commission 1953

2 ———, S W ROOT R M KNISELEY, and H D KERMAN Intracavitary Use of Colloidal Radioactive Gold *Radiology* 61 922 929 1953

3 ANDREWS G A and M P TYOR Early Results of the Treatment of Chronic Granulocytic Leukemia With Intravenous Colloidal Gold 198 *J Lab & Clin Med* 42 777 778 1953

4 BLOCK M H L O JACOBSON and W B NEAL Biologic Studies with Arsenic [6] upon the Clinical Course of Patients with Tumors of the Hematopoietic Tissues *J Lab & Clin Med* 34 1336 1375 1949

5 *Brookhaven Conference Report* BNL-C 5 July 1948

6 DUCOFF H S W B NEAL R L STRAUBE, L O JACOBSON and A M BRUES Biologic Studies with Arsenic [6] II Excretion and Tissue Localization *Proc Soc Exper Biol & Med* 69 584 554 1948

7 EVANS T C M LENZ, C P DOULAN and M J LEMAY Effects of Radioactive Sodium on Leukemia and Allied Diseases *Am J Roentgenol* 59 469-481, 1948

8 FARR L E W H SWEET J S ROBERTSON C G FOSTER H B LOCKSLEY D L SUTHERLAND, M L MENDELSON and E E STICKLEY Neutron Capture Therapy with Boron in the Treatment of Glioblastoma Multiforme *Am J Roentgenol* 71 279 291 1954

9 FLOCKS R H H D KERR H B ELKINS and D CULP Treatment of Carcinoma of the Prostate by Interstitial Radiation with Radioactive Gold (Au 198) A Preliminary Report *J Urol* 68 510 522 1952

10 HAHN P F *A Manual of Artificial Radioisotope Therapy* 1st ed New York Academic Press Inc 1951 pp 87 93

11 ——— Tumor Therapy by the Direct Infiltration of Radioactive Colloidal Metallic Gold *Federation Proc* 7 371 1948

12 HAMILTON J G and R S STONE Intravenous and Intraduodenal Administration of Radiosodium *Radiology* 28 178 188, 1937

13 HARPER P V and K A LATHROP Isotope Therapy for Intra abdominal Tumors *Argonne Cancer Research Hospital Semiannual Report to the Atomic Energy Commission* pp 54 61 Sept 1954

14 LANG F R A Study of the Use of Radioactive Gallium in Medicine *Am Int Med* 35 1237 1249 1951

15 LAWRENCE J H K G SCOTT and L W TUTTLE Studies on Leukemia with the Aid of

Radioactive Phosphorus *Internat Clin* 3 33 58 1939

16 LAWRENCE J H R LOWRY B V LOW BEER and B BROWN Chronic Myelogenous Leukemia A Study of 129 Cases in which Treatment was with Radioactive Phosphorus *J A M A* 136 672 677 1948

17 MARINELLI L D Dosage Determination with Radioactive Isotopes *Am J Roentgenol* 47 210 216 1942

18 McCONAHEY W M F R KEATING and M H POWER The Behavior of Radioiodine in the Blood *J Clin Invest* 28 191 198 1949

19 RASMUSSEN T B P V HARPER E YUHL and D M BERGENSTAL The Destruction of the Pituitary Gland in Metastatic Cancer with Yttrium 90 Pellets *Argonne Cancer Research Hospital Semiannual Report to the Atomic Energy Commission* pp 1 16 March 1955

20 REINHARD E H C V MOORE C S BIERBAUM and S MOORE Radioactive Phosphorus as a Therapeutic Agent A Review of the Literature and Analysis of the Results of Treatment of 155 Patients with Various Blood Dyscrasias Lymphomas and Other Malignant Neoplastic Diseases *J Lab & Clin Med* 31 107 218 1946

21 SHERMAN A I M BONEBRAKE and W M ALLEN The Application of Radioactive Colloidal Gold in the Treatment of Pelvic Cancer *Am J Roentgenol* 66 624 628 1951

22 STANLEY M M and E B ASTWOOD Accumulation of Radioactive Iodide by Thyroid Gland in Normal and Thyrotoxic Subjects and Effect of Thiocyanate on its Discharge *Endocrinology* 42 107 123 1948

23 THYGESEN J C A VIDEBOECK and I VILLAUME Treatment of Leukemia with Radioactive Sodium *Acta radiol* 25 305 316 1944

CHAPTER 26A

1 COLMERY B H JR Preparation of Seeds of Radioactive Gold 198 and Their Use in Cancer Therapy *M Sc Thesis* The Ohio State University 1951

2 HENSCHKE U K Interstitial Implantation with Radioisotopes *in Therapeutic Use of Artificial Radioisotopes* P F HAHN (ed) New York John Wiley & Sons Inc 1956

3 —— A G JAMES and W G MYERS Radiogold Seeds in Clinical Radiation Therapy *Radiology* 63 390 1954

4 —— —— and —— Radiogold Seeds for Cancer Therapy *Nucleonics* 11 46 1953

5 JAMES A G U K HENSCHKE and W G MYERS The Clinical Use of Radioactive Gold (Au 198) Seeds *Cancer* 6 1034 1953

6 —— R D WILLIAMS and J L MORTON The use of Radioactive Cobalt in Non resectable Head and Neck Cancer *Cancer* 4 1333 1951

7 —— —— and —— Radioactive Cobalt as an Adjunct to Cancer Surgery *Surgery* 30 95 1951

8 McLELLON W M The Use of Radioactive Gold 198 for the Treatment of Malignancies *M Sc Thesis* The Ohio State University 1952

9 MORTON J L G W CALLENDINE JR and W G MYERS Radioactive Cobalt 60 in Plastic Tubing for Interstitial Radiation Therapy *Radiology* 506 553 1951

10 MYERS W G Applications of Artificial Radioisotopes in Interstitial Radiation Therapy *Proceedings of 2nd National Cancer Conference* Vol 2 p 1652 New York American Cancer Society Inc 1952

11 —— B H COLMERY JR and W M McLELLON Radioactive Gold 198 for Gamma Radiation Therapy *Am J Roentgenol* 70 258 1953

12 —— and —— Radioactive Au 198 in Gold Seeds for Cancer Therapy *Cancer Res* 12 285 1952

13 SINCLAIR W K Artificial Radioactive Sources for Interstitial Therapy *Brit J Radiol* 25 417 1952

CHAPTER 26B

1 GREENBERG JOSEPH H C DUDLEY and S S SARKISIAN A Study of Methods for Interstitial Implantation of Radioactive Material II Filaments Containing Yttrium 90 *Am J Roentgenol* 77 852 1957

CHAPTER 27

1 BARNES A C J L MORTON and G W CALLENDINE The Use of Radioactive Cobalt in the Treatment of Carcinoma of the Cervix *Am J Obst & Gynec* 60 1112 1950

2 CALLENDINE G W J L MORTON and W G MYERS Physical Considerations in Applying Cobalt^{60} to Cancer Therapy *Nucleonics* 7 63 1950

3 DEUTSCH M L G ELLIOTT and A ROBERTS Disintegration Schemes of Radioactive Substances VIII Cobalt^{60} *Physics Review* 68 193 1945

4 JAMES A G R G WILLIAMS and J L MORTON Radioactive Cobalt in Head and Neck in Inoperable Head and Neck Surgery Read Before the James Ewing Society at Memorial Hospital New York March 17 1951

5 —— —— and —— Radioactive Cobalt as an Adjunct to Cancer Surgery *Surgery* 30 95 1951

6 —— —— and —— The Use of Radioactive Cobalt in Non Resectable Head and Neck Cancer *Cancer* 4 1333 1951

7 LIVINGOOD J H and G T SEABORG Radioactive Isotopes of Cobalt *Physics Review* 60 913 1941

8 MAYNEORD W V and A J CIPRIANI Some Applications of Nuclear Physics to Medicine *Brit J Research* (Supp 2) 1950

9 —— and —— Absorption of Gamma Rays from Cobalt^{60} *Canad J Research (Supp 2)* 25 503 1947

10 MESCHAN I G REGNIER J W NELSON and A W LAFFERTY Dosage Tables for Cobalt^{60} for Use with Interstitial Plaque and Intracavitary Applications *Am J Roentgenol* 71 320 1954

11 —— R R EDWARDS and P J ROSENBAUM Practical Physical Aspects in Use of Radioactive Cobalt^{60} as Radium Substitute *Am J Roentgenol* 65 255 1951

12 —— A NETTLESHIP and E S KEREKES Comparative Skin Effects of Identical

Gamma Roentgen Doses of Cobalt 60 and Radium *Exhibit* at the Thirty sixth Annual Meeting of the Radiological Society of North America 1950

13 Mitchell J S Applications of Recent Advances in Nuclear Physics to Medicine with Special Reference to Pile and Cyclotron as Sources of Radioactive Isotopes *Brit J Radiol 19* 481 1946

14 Morton J L G W Callendine and W G Myers Cobalt 60 Nylon Thread a New Interstitial Radiation Therapy *Paper and exhibit* presented at the Thirty sixth Annual Meeting of the Radiological Society of North America 1950

15 ——— ——— and ——— Flexible Thread Source of 1 25 Million Volt Gamma Rays for Therapy *Cancer Res 11* 270 1951

16 ——— A C Barnes C H Hendricks, and G W Callendine Use of Interstitial Applicators in Treatment of Carcinoma of the Cervix Uteri *Read at Radium Society* at Atlantic City New Jersey 1951

17 ——— G W Callendine and W G Myers Radioactive Cobalt 60 in Plastic Tubing for Interstitial Radiation Therapy *Radiology 56* 553 1951

18 ——— A C Barnes and G W Callendine Individualized Interstitial Treatment of Cancer of the Uterine Cervix Using Cobalt 60 in Needles Inserted Through a Lucite Template *Am J Roentgenol 65* 737 1951

19 Myers W G Applications of Artificially Radioactive Isotopes in Therapy *Am J Roentgenol 60* 816 1948

20 Paterson R and H M Parker Dosage System for Gamma Ray Therapy Part I and Part II *Brit J Radiol 2* 252 313 1938

21 ——— and ——— Dosage System for Interstitial Radium Therapy Parts I and II *Brit J Radiol 2* 252 313 1938

22 Quimby E H L D Marinelli and J V Blady Secondary Filters in Radium Therapy *Am J Roentgenol 41* 804 1939

23 Risser J R Neutron induced Radioactivity of Long Life in Cobalt *Physics Review 52* 768 1931

24 Stewart F S Contribution to Discussion on Dosage Control in Interstitial Radium Therapy *Brit J Radiol 19* 142 1946

CHAPTER 28

1 Brucer Marshall W G Pollard H Leiter and H Scarf Shaped Sources for Teletherapy Units *Nucleonics 11* 38 1953

2 ——— Evaluation of Teletherapy Sources *Nucleonics 10*·9 1952

3 ——— New Developments in Teletherapy *Nucleonics 10* 40 1952

4 Deutsch M L G Elliott and A Roberts Disintegration Schemes of Radioactive Substances VIII Cobalt 60 *Phys Rev 68* 193 1945

5 Dixon W R C Garrett and A Morrison Radiation Measurements with the Eldorado Cobalt 60 Teletherapy Unit *Brit J Radiol 25* 314 1952

6 ——— ——— and ——— Room Protection Measurements for Cobalt 60 Teletherapy Units *Nucleonics 10* 42 1952

7 Evans R D Radioactivity Units and Standards *Nucleonics 1* 32 1947

8 Fedoruk S O H E Johns and T A Watson Isodose Distributions for a 1100 Curie Cobalt 60 Unit *Radiology 60* 348 1953

9 Fermi E E Amaldi O d Agostino F Rasetti and E Segre Artificial Radioactivity Produced by Neutron Bombardment II *Proc Roy Soc (London) 149* 522 1935

10 Green D T and R F Errington Considerations in Design of Cobalt 60 Beam Therapy equipment *J Canad A Radiol 3* 20 1952

11 ——— ——— F Boyd and N Hopkins Production of Multicurie Gamma Ray Teletherapy Sources *Nucleonics 11* 29 1953

12 ——— and ——— Design of a Cobalt 60 Beam Therapy Unit *Brit J Radiol 25* 309 1952

13 Grimmett L G H D Kerman M Brucer G H Fletcher and J F Richardson Design and Construction of a Multicurie Cobalt Teletherapy Unit *Radiology 59* 19 1952

14 Hare H F S W Lippincott D Sawyer and J G Trump Physical and Clinical Aspects of Supervoltage Rotational Therapy *Radiology 57* 157 1951

15 ——— J G Trump E W Webster Rotational Scanning of Breast Malignancies *Am J Roentgenol 68* 435 1952

16 Howarth J L A Technique for Beam Direction with a 2 Mev X Ray Generator *Brit J Radiol 26* 149 1953

17 Johns H E Physical Characteristics of the Radiation in Cobalt 60 Beam Therapy *J Canad A Radiol 3* 2 1952

18 ——— L M Bates and T A Watson 1000 Curie Cobalt Units for Radiation Therapy *Brit J Radiol 25* 296 1952

19 ——— E R Epp D V Cormack and S O Fedoruk Depth Dose Data and Diaphragm Design for the Saskatchewan 1000 Curie Cobalt Unit *Brit J Radiol 25* 302 1952

20 ——— *et al* 1000 Curie Cobalt 60 Units for Radiation Therapy *Nature London 168* 1035 Dec 15 1951

21 Kennedy R J H O Wyckoff and W A Snyder Concrete as a Protective Barrier for Gamma Rays from Cobalt 60 *J Research Nat Bureau of Stand* vol 44 February 1950

22 Leucutia T Teletherapy with Various Radioactive Sources *Am J Roentgenol 69* 108 1953

23 Livingood J J F Fairbrother and G T Seaborg Radioactive Isotopes of Manganese Iron and Cobalt *Phys Rev 52* 135 1937

24 ——— and G T Seaborg Long lived Radio Cobalt Isotopes *Phys Rev 53* 847 1938

25 ——— and ——— Radioactive Isotopes of Cobalt *Phys Rev 60* 1913 1941

26 Lockett E E and R H Thomas The Half Lives of Several Radioistopes *Nucleonics 11* 14 1953

27 Mayneord W V Energy Absorption *Brit J Radiol 13* 235 1940

28 ——— Therapeutic Gamma Ray Sources *National Research Council of Canada Report No MM—237* March 1946

29 ——— Some Applications of Nuclear Physics to Medicine *Brit J Radiol* Supplement No 2 180 1950

30 MILLER H A 2 Mev X Ray Generator for Therapy *Brit J Radiol 23* 731 1950
31 MITCHELL J S Applications of Recent Advances in Nuclear Physics to Medicine *Brit J Radiol 19* 481 1946
32 MYERS N G Radioactive Isotopes in Therapy I Cobalt 60 *Radiology 60* 816 1948
33 NELSON M E M L POOL and J D KURBATOV The Characteristic Radiations of Cobalt 60 *Phys Rev 62* 1 1942
34 PATERSON R *The Treatment of Malignant Disease by Radium and X Rays* London Edward Arnold and Co 1948
35 PHILLIPS R *Supervoltage X Ray Therapy* London H K Lewis and Co Ltd 1944
36 RISSER J R Neutron induced Radioactivity of Long Life in Cobalt *Physics Rev 52* 768 1937
37 SAMPSON M B L N RIDENOUR and W BLEAKNEY The Isotopes of Cobalt and Their Radioactivity *Phys Rev 50* 382 1936
38 SCHULTZ M D Supervoltage Roentgen Therapy in Mouth and Throat *Radiology 55* 52 1950
39 SMITH I H Cobalt 60 Beam Therapy Some Influences and Advantages *J Canad A Radiol 3* 16 1952
40 SPIERS F W Effective Atomic Number and Energy Absorption in Tissues *Brit J Radiol 19* 52 1946
41 STEED P R Three Dimensional Dose Distribution with Rotation Techniques *Brit J Radiol 26* 65 1953
42 TRUMP J G Physical Basis for High Skin Tolerance of Supervoltage Roentgen Rays *Radiology 50* 649 1948
43 ——— K A WRIGHT W W EVANS H F HARE and S W LIPPINCOTT Two Million Volt Roentgen Ray Therapy Using Rotation *Am J Roentgenol 66* 613 1951
44 WATSON T A Clinical Possibilities of Cobalt 60 Beam Unit *J Canad A Radiol 3* 7 1952
45 WILSON C W and B J PERRY Physical Observations Relating to the 2 Mev Van de Graff Electrostatic Generator at Westminster Hospital *Brit J Radiol 25* 210 1952

CHAPTER 29

1 AMERICAN RADIUM SOCIETY The Indiscriminate Use and Rental of Radium *Am J Roentgenol 32* 251 1934
2 AMERICAN STANDARDS ASSOCIATION WAR COMMITTEE ON SAFETY CODE FOR THE INDUSTRIAL USE OF X RAYS *Safety Code for the Industrial Use of X Rays* New York American Standards Association 1946
3 ARDRAN G M Dose Reduction in Diagnostic Radiology *Brit J Radiol 30* 436 1957
4 ——— and H E CROOKS Gonad Radiation Dose from Diagnostic Procedures *Brit J Radiol 30* 295 1957
5 BATELLI F *Cited by* Brown [8]
6 BRAESTRUP C B X ray Protection in Diagnostic Radiology *Radiology 38* 207 1942
7 ——— and H O WYCKOFF Protection Requirements of One Million Volt and Two Million Volt Roentgen Ray Installations *Radiology 51* 840 1948
8 BROWN P *American Martyrs to Science through the Roentgen Rays* Springfield Ill Charles C Thomas 1936
9 BRUCER M Teletherapy Design Problems *Radiology 62* 91 1954
10 BUREAU OF STANDARDS *Roentgen Ray Protection* Circular No C404 1933
11 CASSEN B K E CORRIGAN and H S HAYDEN Attenuation and Transition Effects in the Absorption of Supervoltage Radiation *Radiology 31* 319 1938
12 CHAOUL H and A ADAM Die Rontgen Nahbestrahlung maligner Tumoren *Strahlentherapie 48* 31 1933
13 CILLEY E I L E T LEDDY and B R KIRKLIN The Dangers of Roentgenoscopy and Methods of Protection Against Them *Am J Roentgenol 32* 360 1934
14 DIXON W F C GARRETT and A MORRISON Room Protection Measurements for Cobalt 60 Teletherapy Units *Nucleonics 10* 42 1952
15 ERNST H W and P OTT Die vom Patienten ausgehende Streustrahlung bei Tiefentherapie *Strahlentherapie 53* 595 1935
16 EVANS R D Radium Poisoning II The Quantitative Determination of the Radium Content and Radium Elimination Rate of Living Persons *Am J Roentgenol 37* 368 1937
17 EVANS W W R C GRONKE K A WRIGHT and J G TRUMP Absorption of 2 Mev Constant Potential Roentgen Rays by Lead and Concrete *Radiology 58* 560 1952
18 FAILLA G Radium Protection *Radiology 19* 12 1932
19 ——— Protection Against High Energy Roentgen Rays Caldwell Lecture 1945 *Am J Roentgenol 54* 553 1945
20 ——— and PATRICIA MCCLEMENT The Shortening of Life by Chronic Whole Body Irradiation *Am J Roentgenol 78* 946 1957
21 ——— E H QUIMBY L D MARINELLI and J E ROSE The Relative Effects Produced by 200 Kv Roentgen Rays 700 Kv Roentgen Rays and Gamma Rays I The Distribution of Radiation in a Water Phantom *Am J Roentgenol 29* 293 1933
22 FEDDEMA J and W J OOSTERKAMP Volume Dose in Diagnostic Radiology *In* J W McLaren (ed) *Modern Trends in Diagnostic Radiology* New York Paul B Hoeber Inc 1953 Chap 4
23 FOLSOM T R and E F FOCHT Data on the Attenuation of Narrow and Broad Beams of 1 000 Kilovolt (Peak) Roentgen Rays by Lead Concrete and Water *Am J Roentgenol 51* 76 1944
24 GLASS B The Genetic Basis for the Limitation of Radiation Exposure *Am J Roentgenol 78* 955 1957
25 GLASSER O *Wilhelm Conrad Rontgen und die Geschichte der Roentgenstrahlen* Berlin Springer 1931
26 HAMILTON J G Metabolism of Fission Products and the Heaviest Elements *Radiology 49* 325 1947
27 HENSHAW P S Further Problems in X Ray Protection II Irradiation Injury and the Tolerance Dose *Radiology 44* 569 1945
28 HICKEY P M The First Decade of American Roentgenology *Am J Roentgenol 20* 150 1928

29 HOL R and K KOREN Protection Measures in Roentgen Diagnostics with Reference to Doses Inducing Mutations *Acta radiol* 44 471 1955
30 International Recommendations for X Ray and Radium Protection *Radiology* 23 682, 1934
31 KAYE G W C. The Story of Protection *Radiography* 6 41 1940
32 ——— H BEHNKEN E PUGNO VANONI I SOLOMON and L S TAYLOR International Recommendations for X Ray and Radium Protection Revised by the International X Ray and Radium Protection Committee at the Fifth International Congress of Radiology Chicago September 13 17 1937 *Am J Roentgenol* 40 134 1938
33 LAUGHLIN J S M L MEURK I PULLMAN and R S SHERMAN Bone Skin and Gonadal Doses in Routine Diagnostic Procedures *Am J Roentgenol* 78 961 1957
34 MARTIN J H Radiation Doses Received by the Skin of a Patient During Routine Diagnostic X ray Examinations *Brit J Radiol* 20 279 1947
35 National Bureau of Standards Handbook 42 Safe Handling of Radioactive Isotopes Washington D C Superintendent of Documents Government Printing Office 1949
36 National Bureau of Standards Handbook 51 Radiological Monitoring Methods and Instruments Washington D C Superintendent of Documents Government Printing Office 1954
37 National Bureau of Standards Handbook 54 Protection Against Radiations from Radium Cobalt 60 and Cesium 137 Washington D C Superintendent of Documents Government Printing Office 1954
38 National Bureau of Standards Handbook 59 (Insert) Permissible Dose from External Sources of Ionizing Radiation Washington D C Superintendent of Documents Government Printing Office 1954
39 National Bureau of Standards Handbook 60 X ray Protection Washington D C Superintendent of Documents Government Printing Office 1955
40 PERUSSIA F and E PUGNO VANONI *Trattato di Roentgen e di Curie terapia* Milano Fratelli Treves 1934
41 QUIMBY E H and E F FOCHT Dosage Measurements in Contact Roentgen Therapy *Am J Roentgenol* 50 653 1943
42 ——— R S STONE P S HENSHAW R B TAFT G C HENNY G SINGER and G C LAURENCE Protection Against X Rays and Gamma Rays a Combined Report on the Standardization Committee of the American Roentgen Ray Society and The Radiological Society of North America *Radiology* 46 57 1946
43 RITTER F W S R WARREN and E P PENDERGRASS Roentgen Doses During Diagnostic Procedures *Radiology* 59 238 1952
44 ROLLINS W *Cited* by Taylor [60]
45 RÖNTGEN W C *Cited* by Glasser [25]
46 RUSS S *Cited* by Taylor [60]
47 ——— and G M SCOTT Some Biological Effects of Continuous Gamma Irradiation with a Note on Protection *Brit J Radiol* 10 619 1937
48 SAENGER E L Emergency Measures and Precautions in Radium Accidents *J.A.M.A* 149 813 1952
49 SANFORD A H C SHEARD and A E OSTERBERG The Photelometer and Its Use in the Clinical Laboratory *Am J Clin Path* 3 405 1933
50 SAX N I *Handbook of Dangerous Materials* New York Reinhold Publishing Corporation 1951 p 236
51 SIEVERT R M On Protection Against Radiation in Teleradium Treatment *Acta radiol* 14 597 1933
52 SINGER G L S TAYLOR and A L CHARLTON Concrete as a Protective Material Against High Voltage X Rays *Radiology* 33 68 1939
53 SOLOMON I *Précis de radiothérapie profonde* Paris Masson et Cie 1926
54 STENSTROM K W Protection in X Ray Therapy *Radiology* 19 7 1932
55 ——— and C E NURNBERGER Protective Factors in the Preparation and Handling of Gold Implants and Other Radon Applicators *Am J Roentgenol* 37 247 1937
56 STONE R S Common Sense in Radiation Protection Applied to Clinical Practice *Am J Roentgenol* 78 993 1957
57 TAFT R B Protective Cover for Tube Bowl *Am J Roentgenol* 28 562 1932
58 TAYLOR L S Roentgen Ray Protection *Am J Roentgenol* 22 45 1929
59 ——— The Work of the National and International Committees on X Ray and Radium Protection *Radiology* 19 1 1932
60 ——— Roentgen ray Protection" in *The Science of Radiology* Springfield Ill Charles C Thomas 1933 p 332
61 TAYLOR L S Practical Suggestions for Reducing Radiation Exposure in Diagnostic Examinations *Am J Roentgenol* 78 983 1957
62 THORAEUS R The Protective Power of Lead Rubber *Acta radiol* 14 424 1933
63 TROUT E D and R M GAGER. Protective Materials for Field Definition in Radiation Therapy *Am J Roentgenol* 63 396 1950
64 WERNER W S X Ray Protection from the Manufacturer s Viewpoint *Radiology* 19 5 1932
65 WOOD F C Protection of Patients and Operators from X Rays *J A.M.A* 96 1760 1931

CHAPTER 30

1 ACKERMAN L V and J A DEL REGATO *Cancer Diagnosis Treatment and Prognosis* St Louis C V Mosby Co 1947
2 ARIEL I M The Effect of Single Massive Doses of Roentgen Radiation upon the Liver *Radiology* 57 561 1951
3 BUIE L. A and G E MALMGREN Factitial Proctitis a Justifiable Lesion Observed in Patients Following Irradiation *Internat Clin* 3 68 1930
4 GLASSER O E H QUIMBY L S TAYLOR and J L WEATHERWAX *Physical Foundations of Radiology* 2nd ed New York Paul B Hoeber Inc 1952
5 JONES T E Benign Stricture of the Intestine Due to Irradiation *S Clin North America* 19 1185 1939
6 LEUCUTIA T Factitial Reactions in Con

nection with Irradiation to the Pelvis *Am J Roentgenol 53* 180 1945

7 MacKee F M and A C Cipollaro *X Rays and Radium in Treatment of Diseases of the Skin* 4th ed Philadelphia Lea and Febiger 1947

8 Martin C L and F T Rogers Roentgen Ray Cachexia *Am J Roentgenol 11* 280 1924

9 McIntosh H C and J E Hutton Clinical and Roentgen Aspects of Irradiation Stricture of the Rectum and Sigmoid Its Course and Treatment *Am J Roentgenol 52* 647 1944

10 Pack G T and E M Livingston (eds) *Treatment of Cancer and Allied Diseases* 1st ed New York Paul B Hoeber Inc 1940

11 Paterson R *The Treatment of Malignant Disease by Radium and X Rays* London Edward Arnold & Co 1951

12 Phillips R X Ray to the Liver for Metastatic Cancer *Paper delivered before the American Radium Society* April 21 1953

13 Pohle E A (ed) *Clinical Radiation Therapy* Philadelphia Lea and Febiger 1950

14 Portmann U V (ed) *Clinical Therapeutic Radiology* New York Thomas Nelson and Sons 1950

15 White W C and F W Finn The Late Complications Following Irradiation of Pelvic Viscera *Am J Obst & Gynec 62* 65 1951

16 Wiley H M and E D Sugarbaker Roentgenotherapeutic Changes in the Small Intestine Surgical Aspects *Cancer 3* 629 1950

Bibliography for Addendum

1 Allen J G B J Grossman R M Elghammer P V Moulder C L McKeen L O Jacobson M Pierce T R Smith and J M Crosbie Abnormal Bleeding Response to Treatment with Toluidine Blue and Protamine Sulfate *J A M A 139* 1251 1949

2 Allen J G P V Moulder and D M Emerson Pathogenesis and Treatment of the Postirradiation Syndrome *J A M A 145* 704 1951

3 Allen J G M Sanderson M Milham A Kirschon and L O Jacobson Heparinemia (?) An Anticoagulant in the Blood of Dogs with Hemorrhagic Tendency After Total body Exposure to Roentgen Rays *J Exper Med 87* 71 1948

4 Bennett L R P E Rekers M Kresge and J W Howland The Influence of Infection on the Hematological Effects and mortality following Mid lethal X radiation UR 76 May 24 1949 b (unclassified)

5 Bloom W and L O Jacobson Some Hematologic Effects of Irradiation *Blood 3* 586 1948

6 Burnett W T G E Stapleton and A Hollaender Protective Action of Some Sulfur containing and Sulfur free Compounds Against X ray Damage in Bacteria *Federation Proc 10* 32 1951

7 Chapman W H C R Sipe D C Eltzholtz E P Cronkite and F W Chambers Sulphydryl-containing Agents and the Effects of Ionizing Radiations I Beneficial Effect of Glutathione Injection on X ray Induced Mortality Rate and Weight Loss in Mice Naval Medical Research Institute NM 006 012 08 25 1949

8 Cronkite E P The Hemorrhagic Syndrome of Acute Ionizing Radiation Illness Produced in Goats and Swine by Exposure to the Atomic Bomb at Bikini 1946 *Blood 5* 32 1950

9 ——— D C Eltzholtz C R Sipe W H Chapman and F W Chambers Failure of Rutin to Decrease the Mortality of Acute Ionizing Radiation in Mice Naval Medical Research Institute NM 007 039 Report 16 1948 a

10 Dowdy A H L R Bennett and S M Chastain Protective Action of Anoxic Anoxia Against Total Body Roentgen Irradiation of Mammals *Radiology 55* 879 1950

11 Ellinger F Some Effects of Desoxycorticosterone Acetate on Mice Irradiated with X rays *Proc Soc Exper Biol & Med 64* 31 1947

12 ——— Influence of Pharmacological Agents on Effects of Irradiation *Radiology 50* 234 1948

13 Evans T C W A Robbie J P Goodrich and J C Slaughter Low Temperature and the Radiosensitivity of Skin of New born Rats II Resistance at Different Dosages *Proc Soc Exper Biol & Med 46* 662 1941

14 Field J B and P E Rekers Studies of the Effects of Flavonoids on Roentgen Irradiation Disease II Comparison of the Protective Influence of Some Flavonoids and Vitamin C in Dogs *J Clin Invest 28* 746 1949

15 Fredell H M Sanderson A Kirschon M Milham and J G Allen The Effects of X rays on Antibodies Argonne National Laboratory ANL 4078 1947

16 Graham J B and R M Graham Pharmacological Modification of Resistance to Radiation *Proc Nat Acad Sc 35* 102 1949

17 Griffin A C and E L Brandt Effect of Cysteine in Reducing the Toxicity of Nitrogen Mustards *Federation Proc 10* 192 1951

18 Hempelmann L H H Lisco and J G Hoffman The Acute Radiation Syndrome A Study of Nine Cases and a Review of the Problem *Ann Int Med 36* 279 1952

19 Howland J T F Furth L R Bennett M Coulter and G M McDonnel Studies of Factors Affecting the Radiation Syndrome I The Effect of Aureomycin and Antibiotics on Whole body Irradiation University of Rochester Atomic Energy Project UR 94 Oct 14 1949

20 Jacobson L O E L Simmons E K Marks and E O Gaston Further Studies on Recovery from Irradiation *J Lab & Clin Med 37* 683 1951

21 Patt H M R L Straube E B Tyree M N Swift and D E Smith Influence of Estrogens on the Acute X irradiation Syndrome *Am J Physiol 159* 269 1949

22 Patt H M E B Tyree R L Straube and D F Smith Cysteine Protection Against X irradiation *Science 110* 213 1949

23 Rekers P F and J B Field Control of Hemorrhagic Syndrome and Reduction of X irradiation Mortality with a Flavone *Science 107* 16 1948

24 Rekers P E M P Coulter and S L Warren Effect of Transplantation of Bone Marrow into Irradiated Animals *A M A Arch Surg 60* 635 1950

25 Simmons E L L O Jacobson N

PEARLMAN and C L PROSSER The Effectiveness of Drugs in Preventing or Alleviating X ray Damage MDDC 1277 Oct 1946
26 STRAUBE R L H M PATT E B TYREL and D E SMITH Influence of Level of Adrenal Cortical Steroids on Sensitivity of Mice to X irradiation *Proc Soc Exper Biol & Med 71* 539 1949
27 ZIRKLE R E Modification of Radiosensitivity by Means of Readily Penetrating Acids and Bases *Am J Roentgenol 35* 230 1936

CHAPTER 31

1 ADAIR F E R C MELLORS J H FARROW H Q WOODARD G C ESCHER and J A URBAN The Use of Estrogens and Androgens in Advanced Mammary Cancer *J A M A 140* 1193 1949
2 ALBRIGHT F The Effect of Hormones on Osteogenesis in Man In *Recent Progress in Hormone Research* G PINCUS (ed), New York Academic Press Inc 1947 vol 1 p 293
3 ASTWOOD E B C F GESCHICKTER and E O RAUSCH Development of the Mammary Gland of the Rat *Am J Anat 61* 373 1937
4 BADGER G M L A ELSON A HADDOW C L HEWETT and A M ROBINSON The Inhibition of Growth by Chemical Compounds *Proc Roy Soc London s B 130* 255 1942
5 BALL H A and L T SAMUELS The Relation of the Hypophysis to the Growth of Malignant Tumors III The Effect of Hypophysectomy on Autogenous Tumors *Am J Cancer 26* 547 1936
6 ——— and ——— The Relation of the Hypophysis to the Growth of Malignant Tumors IV A Study of the Influence of Nutritional Factors on Walker Tumor 256 in Relation to the Effect of Hypophysectomy *Am J Cancer 32* 50 1938
7 BEATSON G T On the Treatment of Inoperable Cases of Carcinoma of the Mamma Suggestions for a New Method of Treatment with Illustrative Cases *Lancet 2* 104 162 1896
8 BITTNER J J Studies on Concomitant Immunity *Am J Cancer 28* 121 1936
9 ——— Influences of Breast Cancer Development in Mice *Pub Health Rep 54* 1590 1939
10 ——— The Causes and Control of Mammary Cancer in Mice *Harvey Lect 42* 221 1946 47
11 ——— Some Enigmas Associated with the Genesis of Mammary Cancer in Mice *Cancer Res 8* 625 1948
12 ——— Genetic Aspect of Cancer Research *Am J Med 8* 218 1950
13 ——— R A HUSEBY M B VISSCHER Z B BALL and F SMITH Mammary Cancer and Mammary Structure in Inbred Stocks of Mice and Their Hybrids *Science 99* 83 1944
14 BRENDLER H W E CHASE and W W SCOTT Prostatic Cancer Further Investigation of Hormonal Relationships *A M A Arch Surg 61* 433 1950
15 BURROWS H *Biological Actions of Sex Hormones* 2nd ed London Cambridge University Press 1949 p 443
16 COHEN S L and R A HUSEBY The Effect of Estrogen on the Serum Glucuronidase Activity of Patients with Breast Cancer *Cancer Res 11* 52 1951
17 ——— and R A HUSEBY Inverse Changes of Serum Glucuronidase and Esterase of Breast Cancer Patients on Estrogen Therapy *Proc Soc Exper Biol & Med 76* 304 1951
18 COOK J W and E C DODDS Sex Hormones and Cancer Producing Compounds *Nature 131* 205 1933
19 COOK J W E C DODDS C L HEWETT and W LAWSON The Oestrogenic Activity of Some Condensed Ring Compounds in Relation to Their Other Biological Activities *Proc Roy Soc London s B 114* 272 1934
20 CORI C F Influence of Ovariectomy on Spontaneous Occurrence of Mammary Carcinoma in Mice *J Exper Med 45* 983 1927
21 DEAN A L H Q WOODARD and G H TWOMBLY The Endocrine Treatment of Cancers of the Prostate Gland In *Endocrinology of Neoplastic Diseases A Symposium* G H TWOMBLY and G T PACK (eds) New York Oxford University Press 1947 p 213
22 DEMING C L The Correlation of Clinical Experience and Heterologous Growth of Human Prostatic Cancer *J Urol 61* 281 1949
23 DOUGHERTY T F and A WHITE Effect of Pituitary Adrenotropic Hormone on Lymphoid Tissue *Proc Soc Exper Biol & Med 53* 13[illegible] 1943
24 ——— and ——— An Evaluation of Alterations Produced in Lymphoid Tissue by Pituitary Adrenal Cortical Secretion *J Lab & Clin Med 32* 584 1947
25 FALOON W W L A OWENS M C BROUGHTON and L W GORHAM The Effect of Testosterone on the Pituitary Adrenal Cortex Mechanism in Noncancerous and in Breast Cancer Subjects *J Clin Endocrinol 11* 173 1951
26 FOLEY E J Retardation of Tumor Growth in Mice by Oral Administration of Methyl Androstenediol and Methyl Testosterone *Proc Soc Exper Biol & Med 75* 811 1950
27 GARDNER W U Inhibition of Mammary Growth by Large Amounts of Estrogen *Endocrinology 28* 53 1941
28 ——— Persistence and Growth of Spontaneous Mammary Tumors and Hyperplastic Nodules in Hypophysectomized Mice *Cancer Res 2* 476 1942
29 ——— Tumors in Experimental Animals Receiving Steroid Hormones *Surgery 16* 8 194[illegible]
30 ——— Some Influences of Hormones on the Growth and Persistence of Transplanted Testicular Tumors *Cancer Res 5* 497 1945
31 ——— Studies on Steroid Hormones in Experimental Carcinogenesis In *Recent Progress in Hormone Research* G PINCUS (ed) New York Academic Press Inc 1947 vol [illegible] p 217
32 ——— G M SMITH and L C STRONG Stimulation of Abnormal Mammary Growth by Large Amounts of Estrogenic Hormone *Proc Soc Exper Biol & Med 33* 148 1935
33 GOLDSMITH E D and R F NIGRELLI The Response of the Male Mouse Sex Accessory to Testosterone during Inanition *Tr New York Acad Sc 12* (Ser II) 236 1950
34 GROSS L The Specificity of Acquired Tumor Immunity *J Immunol 50* 91 1945
35 ——— Immunological Relationship

Mammary Carcinomas Developing Spontaneously in Female Mice of a High Tumor Line *J Immunol 55* 297 1947

36 GUTIERREZ R New Horizons in Surgical Management of Carcinoma of the Prostate Gland. *Am J Surg 78* 147 1949

37 HADDOW A Influence of Carcinogenic Compounds and Related Substances on the Rate of Growth of Spontaneous Tumours of the Mouse *J Path & Bact 47* 567 1938

38 ——— and A M ROBINSON The Influence of Various Polycyclic Hydrocarbons on the Growth Rate of Transplantable Tumours *Proc Roy Soc London s B 122* 442 1937

39 ——— C M SCOTT and J D SCOTT The Influence of Certain Carcinogenic and Other Hydrocarbons on Body Growth in the Rat *Proc Roy Soc London s B 122* 477 1937

40 HERTZ R J P YOUNG A G MORROW and W W TULLNER Administration of Massive Dosage of Estrogen to Breast and Prostate Cancer Patients Blood Levels Attained Presented before Section on Experimental Medicine and Therapeutics A M A National Meeting June 1950

41 HESTON W E and H B ANDERVONT Importance of Genetic Influence on the Occurrence of Mammary Tumors in Virgin Female Mice *J Nat Cancer Inst 4* 403 1944

42 ——— M K DERINGER T B DUNN and W D LEVILLAIN Factors in the Development of Spontaneous Mammary Gland Tumors in Agent Free Strain C_3Hb Mice *J Nat Cancer Inst 10* 1139 1950

43 HUGGINS C and D M BERGENSTAL Inhibition of Human Mammary and Prostatic Cancers by Adrenalectomy *Cancer Res 12* 134 1952

44 ——— and C V HODGES Studies on Prostatic Cancer I The Effect of Castration of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate *Cancer Res 1* 293 1941

45 ——— and W W SCOTT Bilateral Adrenalectomy in Prostatic Cancer Clinical Features and Urinary Excretion of 17 Ketosteroids and Estrogens *Ann Surg 122* 1031 1945

46 HUSEBY R A Z B BALL and M B VISSCHER Further Observations on the Influence of Simple Caloric Restriction on Mammary Cancer Incidence and Related Phenomena in C H Mice *Cancer Res 5* 40 1945

47 ——— and J J BITTNER A Comparative Morphological Study of the Mammary Glands with Reference to the Known Factors Influencing the Development of Mammary Carcinoma in Mice *Cancer Res 6* 240 1946

48 ——— and ——— Differences in Adrenal Responsiveness to Post Castrational Alterations as Evidenced by Transplanted Adrenal Tissue *Cancer Res 11* 954 1951

49 ——— and ——— *Unpublished data*

50 ——— and L B THOMAS Histological and Histochemical Alterations in the Normal Breast Tissues of Patients with Advanced Breast Cancer Being Treated with Estrogenic Hormones Cancer January 1954

51 JACOBSEN O Heredity in Breast Cancer a Genetic and Clinical Study of Two Hundred Probands (translated by R Fraser) Contribution 11 in *Nyt Nordisk Forlag* Copenhagen University Institute for Human Genetics 1946

52 JONES E E Tumor Incidence in Line A Albino Mice Following Injections of Progynon B *Am J Cancer 39* 94 1940

53 KEMP T Heredity in Cancer Clinical and Experimental Investigations *Acta path et microbiol scandinav 25* 19 1948

54 KIRSCHBAUM A J R SHAPIRO and H W MIXER Synergistic Action of Estrogenic Hormone and X Rays in Inducing Thymic Lymphosarcoma of Mice *Proc Soc Exper Biol & Med 72* 632 1949

55 ——— W L WILLIAMS and J J BITTNER Induction of Mammary Cancer with Methylcholanthrene I Histogenesis of the Induced Neoplasm *Cancer Res 6* 354 1946

56 KORTEWEG R and F THOMAS Tumor Induction and Tumor Growth in Hypophysectomized Mice *Am J Cancer 37* 36 1939

57 LACASSAGNE A Apparition de cancers de la mamelle chez la souris male soumise a des injections de folliculine *Compt rend Acad d sc 195* 630 1932

58 ——— Relationship of Hormones and Mammary Adenocarcinoma in the Mouse *Am J Cancer 37* 414 1939

59 LATHROP A E C and L LOEB Further Investigations on the Origin of Tumors in Mice III On the Part Played by Internal Secretions in the Spontaneous Development of Tumors *J Cancer Res 1* 1 1916

60 LITTLE C C The Genetics of Cancer in Mice *Biological Reviews 22* 315 1947

61 LUDFORD R J and L DMOCHOWSKI Effect of Stilbestrol on Mouse Tumors *Lancet 2* 718 1947

61*a* LUFT R and H OLIVECRONA Experiences with Hypophysectomy in Man *J Neurosurg 10* 301 1953

62 MCEUEN C S and D L THOMSON The Effect of Hypophysectomy on the Growth of the Walker Rat Tumour *Brit J Exper Path 14* 384 1933

62*a* MUHLBOCK O The Hormonal Genesis of Mammary Cancer in *Advances in Cancer Research* J P Greenstein and A Haddow (eds) New York Academic Press Inc vol 4 1956

63 MUNGER H V Are Some Prostatic Carcinomas Estrogen Dependent? *Tr South Central Section Am Urol Assoc* p 100 1947

64 MURRAY W S Ovarian Secretion and Tumor Incidence *J Cancer Res 12* 18 1928

64*a* NAGAREDA C S and H S KAPLAN Effect of Hypophysectomy and X Radiation on Lymphoid Organs and on the Induction of Lymphoid Tumors in C Bl Mice *Proc Am A Cancer Res 1* 34 1954

65 NATHANSON I T L I ENGEL and R M KELLEY Effects of Androgens on the Urinary Excretion of Ketosteroids Non Ketonic Alcohols and Estrogens *J Clin Endocrinol 12* 1172 1952

66 PENROSE L S H J MACKENZIE and M N KARN A Genetical Study of Human Mammary Cancer *Ann Eugenics 14* 234 1948

67 SALTER W T I F NATHANSON and H WILSON Experimentally Induced Benignancy of Neoplasm V Influence of Hormones on the Host's Resistance to Implanted Neoplasm *Cancer Res 1* 60 1941

68 SAMUELS L T and H A BALL The Relation of the Hypophysis to the Growth of Malignant Tumors II Response of Hypophysectomized Rats to Inoculation with the Walker Transplantable Mammary Carcinoma *Am J Cancer 18* 380 1933
69 ——— J J BITTNER and B K SAMUELS Excretion of Steroids in the Feces of Mice of Various Strains With and Without Mammary Tumor Milk Agent *Cancer Res 7* 722, 1947
70 SEGALOFF A D GORDON B N HORWITT J V SCHLOSSER and P J MURISON Hormonal Therapy in Cancer of the Breast I Effect of Testosterone Propionate Therapy on the Clinical Course and Hormonal Excretion *Cancer 4* 319 1951 II Effect of Methylandrostenediol on the Clinical Course and Hormonal Excretion *Cancer 5* 271 1952
71 SELYE H Experimental Investigations Concerning the Role of the Pituitary in Tumorigenesis *in Endocrinology of Neoplastic Diseases A Symposium* G H TWOMBLY and G T PACK (eds) New York Oxford University Press 1947
72 SMITHERS D W Family Histories of 459 Patients with Cancer of the Breast *Brit J Cancer 2* 163 1948
73 TRENTIN J J and C. W TURNER Quantitative Study of the Effect of Inanition on Responsiveness of the Mammary Gland to Estrogen *Endocrinol 29* 984 1941
74 TRUNNELL J B and B J DUFFY The Influence of Certain Steroids on the Behavior of Human Prostatic Cancer *Tr New York Acad Sc 12* (Ser II) 238 1950
75 WEST C D V P HOLLANDER W F WHITMORE H T RANDALL and O H PEARSON The Effect of Bilateral Adrenalectomy upon Neoplastic Disease in Man *Cancer 5* 1009 1952
76 WOGLOM W H Immunity to Transplantable Tumours *Cancer Review 4* 129 1929
77 ZONDEK B Impairment of Anterior Pituitary Functions by Follicular Hormone *Lancet 2* 842 1936
78 ——— Effect of Prolonged Administration of Estrogen *J A M A 114* 1850 1940

CHAPTER 32

1 ADAIR F E and J B HERRMANN The Use of Testosterone Propionate in Treatment of Advanced Carcinoma of the Breast. *Ann Surg 123* 1023 1946
2 ARIEL I M *Personal Communication*
3 ALLEN E and E A DOISY An Ovarian Hormone Preliminary Report on its Localization Extraction and Partial Purification and Action in Test Animals *J.A M A 81* 819 1923
4 AUCHINCLOSS H and C D HAAGENSEN Cancer of the Breast Possibly Induced by Estrogenic Substances *J.A.M.A 1517* 23 1940
5 ALABEN G and S OWEN Adenocarcinoma of the Breast Coincident with Strenuous Endocrine Therapy *J A M.A 112* 1933 1939
6 BADGER G M L A ELSON A HADDOW C L. HEWETT and A M ROBINSON The Inhibition of Growth by Chemical Compounds *Proc Roy Soc London s.B 130* 255 1942
7 BERKLEY J and R M GRAHAM A Method of Enhancing the Effectiveness of Radiotherapy of the Uterine Cervix *Cancer 6* 68 1953
8 BEATSON, G T On the Treatment of Inoperable Cases of Carcinoma of the Mamma Suggestions for a New Method of Treatment with Illustrative Cases *Lancet 2* 104 162, 1896
9 BEECHAM C T Androgen Therapy in Pelvic Malignancy *Am J Obst & Gynec 46* 849 1943
10 BISKIND M S and M C SHELESNYAK Effect of Vitamin B Complex Deficiency on Inactivation of Ovarian Estrogen in the Liver *Endocrinol 30* 819 1942
11 BRACHETTO-BRIAN D Bases para el Tratamiento Integral del Cancer de la Mama *Prensa méd argent 37*·921 1950
12 BURROWS H *Biological Action of Sex Hormones* London Cambridge University Press 1945
13 CAMPBELL J H and S D CUMMINS Metastases Simulating Mammary Cancer in Prostatic Carcinoma under Estrogenic Therapy *Cancer 4* 303 1951
14 CANTAROW A K. E PASCHKIS A E. RAKOFF and L P HANSEN Studies on Inactivation of Estradiol by the Liver *Endocrinol 33* 309 1943
15 ——— and M TRUMPER *Clinical Biochemistry* 4th ed Philadelphia W B Saunders Co 1949
16 CATCHPOLE H R J B HAMILTON and G R HUBERT The Effect of Male Hormone Therapy on Urinary Gonadotropins in Man. *J Clin Endocrinol 2* 181 1942
17 CHANEY R H and R. B GREENBLATT Palliative Effect of Androgens in Management of Pelvic Malignancies *J M A Georgia 37* 420 1948
18 COLSTON J A and H BRENDLER Endocrine Therapy in Cancer of the Prostate Preparation of Patients for Radical Perineal Prostatectomy *J.A.M A 134* 848 1947
19 CORNER G W and W ALLEN Physiology of Corpus Luteum III Production of Special Uterine Reaction (Progestational Proliferation) by Extracts of Corpus Luteum *Amer J Physiol 880* 326 1929
20 CONWAY H and R B STARK Corticotropin (ACTH) in Treatment of Keloids *Surgery 64* 47 1952
21 COSCADEN J A and S B GUSBERG Background of Cancer of the Corpus *Amer J Obst & Gynec 53* 419 1947
22 COUNCIL ON PHARMACY AND CHEMISTRY Subcommittee on Steroids and Cancer Committee on Research Current Status of Hormone Therapy of Advanced Mammary Cancer *J.A.M.A 146* 471 1951
23 DAMESHEK W M C ROSENTHAL, and L I SCHWARTZ Treatment of Acquired Hemolytic Anemia with Adrenocorticotrophic Hormone (ACTH) *New England J Med 244* 117 1951
24 DAO T L-Y and C HUGGINS Bilateral Adrenalectomy in the Treatment of Cancer of the Breast *A M A Arch Surg 71* 645 1955
25 DAVID K. E DINGEMANSE J FREUD and E LAQUER Über krystallinisches mannliches Hormon aus Hoden (Testosteron) wirksamer als aus Harn oder aus Cholesterin bereitetes Androsteron *Hoppe Seylers Ztschr physiol Chem 233* 281 1935
26 DE COURMELLES F Action atrophique

glandulaire des rayons X *Compt rend Acad d Sc 140* 606 1905

27 DOBRINER K S LIEBERMAN H WILSON M DUNHAM I F SOMERVILLE and C P RHOADS *Adrenal Function and Steroid Excretion in Disease Symposium on Steroids in Experimental and Clinical Practice* ABRAHAM WHITE (ed) New York Blakiston Co 1951 vol 1 p 65

28 DORFMAN R I and R A SHIPLEY *Androgens Biochemistry Physiology and Clinical Significance* New York John Wiley and Sons Inc 1956

29 DOISY E A C D VELER and S THAYER Folliculin from Urine of Pregnant Women *Am J Physiol 90* 329 1929

30 DOUGHERTY T F and A WHITE Effect of Pituitary Adrenotropic Hormone on Lymphoid Tissue *Proc Soc Exper Biol & Med 53* 132 1943

31 DOUGLAS M The Treatment of Advanced Breast Cancer by Hormone Therapy *Brit J Cancer 6* 32 1952

32 ELIEL L P and O H PEARSON The Clinical and Physiological Effects of Adrenocorticotropic Hormone and Cortisone Acetate in Patients with Neoplastic Disease *New York J Med 51* 1839 1951

33 FALLON J J BROSNAN and W MORAN Endometriosis *New England J Med 235* 699 1946

34 FALOON W W L A OWENS M C BROUGHTON and W L GORHAM The Effect of Testosterone on the Pituitary Adrenal Cortex Mechanism in Noncancerous and in Breast Cancer Subjects *J Clin Endocrinol 11* 173 1951

35 FARBER S V DOWNING H SCHWACHMAN R TOCH R APPLETON F HEALD J P KING and D FERIOZI The Action of ACTH and Cortisone on Children with Disseminated Cancer Proceedings of the Second Clinical ACTH Conference *Therapeutics* New York Blakiston Co 1951 vol 2 pp 226 251

36 FARROW J H and H Q WOODARD The Influence of Androgenic and Estrogenic Substances on the Serum Calcium *J A M A 118* 339 1942

37 FEKETE E G WOOLEY and C C LITTLE Histological Changes Following Ovariectomy in Mice I dbe High Tumor Strain *J Exper Med 74* 1 1941

38 FERGUSSON J D and W PAGEL Some Observations on Carcinoma of the Prostate Treated with Oestrogens as Demonstrated by Serial Biopsies *Brit J Surg 33* 122 1945

39 FREED J H E P PENDERGRASS and J W CARNWATH Androgen Therapy in the Control of Pulmonary Metastases from Adenocarcinoma of the Corpus Uteri *Am J Roentgenol 65* 596 1951

40 FREMONT SMITH M J V MEIGS and R M GRAHAM Cancer of the Endometrium and Prolonged Estrogen Therapy *J A M A 131* 805 1946

41 GARLAND L H M BAKER H W PICARD JR and M A SISSON Roentgen and Steroid Hormone Therapy in Mammary Cancer Metastatic to Bone *J A M A 144* 997 1950

42 GASKELL W H *Origin of Vertebrates* New York Longmans Green & Co 1908 p 214

43 GEIST S H J A GAINES and U J SALMON Inhibitory Action of Testosterone Propionate on Human Ovary *Proc Soc Exper Biol & Med 44* 319 1940

44 GELHORN A J HOLLAND J B HERRMANN J MOSS and A SMELIN An Evaluation of Stanalone in the Treatment of Advanced Mammary Carcinoma *J A M A 154* 1274 1954

45 GORDON D B H HORWITT A SEGALOFF P MURISON and J V SCHLOSSER Hormonal Therapy in Carcinoma of the Breast III Effect of Progesterone on Clinical Course and Hormonal Excretion *Cancer 5* 275 1952

46 GRAVES G T and H S HARRIS Carcinoma of the Male Breast with Axillary Metastases Following Stilbestrol Therapy *Ann Surg 135* 411 1952

47 GRIBOFF S J B HERRMANN A SMELIN and J MOSS Hypercalcemia Secondary to Bone Metastases from Carcinoma of the Breast I Relationship Between Serum Calcium and Alkaline Phosphatase Values *J Clin Endocrinol 14* 378 1954

48 GUTIERREZ R New Horizons in Surgical Management of Carcinoma of the Prostate Gland *Am J Surg 78* 147 1949

49 GUTMAN A B and E G GUTMAN An Acid Phosphatase Occurring in the Serum of Patients with Metastasizing Carcinoma of the Prostate Gland *J Clin Invest 17* 473 1938

50 HADDOW A J M WATKINSON E PATTERSON and P C KOLLER Influence of Synthetic Oestrogens upon Advanced Malignant Disease *Brit M J 2* 393 1944

51 HAINES W H and S MICELI Clinical Observations on Estrogenic Therapy in Prostatic and Bladder Carcinoma and Benign Prostatism *Pennsylvania M J 46* 1025 1943

52 HALBERSTAEDTER L and A HOCHMAN Artificial Menopause and Cancer of the Breast *J A M A 131* 810 1946

53 HAMBLEN E C W K CUYLER and M BAPTIST Urinary Excretion of 17 Ketosteroids in Ovarian Failure 3 In Amenorrhea *J Clin Endocrinol 1* 774 1941

54 HARRISON J H G W THORN and D JENKINS Total Adrenalectomy for Reactivated Carcinoma of the Prostate *New England J Med 248* 86 1953

55 HERBST W P Present Picture in Chemotherapy of Prostatic Cancer *J Urol 57* 296 1947

56 HERRELL W E The Relative Incidence of Oophorectomy in Women With and Without Carcinoma of the Breast *Am J Cancer 29* 659 1937

57 HERRMANN J B and F E ADAIR The Effect of Testosterone Propionate on Carcinoma of the Female Breast with Soft Tissue Metastases *J Clin Endocrinol 6* 769 1946

58 ——— F E ADAIR and H Q WOODARD Effects of Estrogenic Hormone on Advanced Carcinoma of the Female Breast *A M A Arch Surg 54* 1 1947

59 ——— ——— and ——— The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast II The Treatment of Osseous Metastases *Surgery 22* 101 1947

60 ——— F KIRSTEN and J S KRAKAUER Hypercalcemic Syndrome Associated With An

drogenic and Estrogenic Therapy *J Clin Endocrinol 9* 1 1949
61 ——— Hormonal Therapy of Breast Cancer *Am J Roentgenol 63* 326 1950
62 ——— The Effect of Hormonal Imbalance on Advanced Carcinoma of the Male Breast *Ann Surg 133* 191 1951
63 ——— *Unpublished data*
64 HERTZ R The Quantitative Relationship Between Stilbestrol Response and Dietary Folic Acid in the Chick *Endocrinol 37* 1 1945
65 ——— J K CROMER J P YOUNG and B B WESTFALL Observations on the Effect of Progesterone on Carcinoma of the Cervix *in Symposium on Steroids in Experimental and Clinical Practice* Philadelphia Blakiston Co 1951 ch 22 p 365
66 HIRST J C Conservative Treatment and Therapeutic Test for Endometriosis by Androgens *Am J Obst & Gynec 53* 483 1947
67 HORSLEY J S Bilateral Oophorectomy With Radical Operation for Cancer of Breast *Surgery 15* 590 1944
68 ——— Treatment of Cancer of Breast in Premenopausal Patients with Radical Amputation and Bilateral Oophorectomy *Ann Surg 125* 703 1947
69 HUGGINS C and P J CLARK Quantitative Studies of Prostatic Secretion II Effect of Castration and of Estrogen Injection on Normal and on Hyperplastic Prostate Gland of Dogs *J Exper Med 72* 747 1940
70 ——— R E STEVENS JR and C V HODGES Studies on prostatic cancer Effects of Castration on Advanced Carcinoma of Prostate Gland *A M A Arch Surg 43* 209 1941
71 ——— Bilateral Adrenalectomy in Prostatic Cancer Clinical Features and Urinary Excretion of 17 Ketosteroids and Estrogen *Ann Surg 122* 1031 1945
72 ——— Prostatic Cancer Treated by Orchiectomy The Five Year Results *J A M A 131* 576 1946
73 ——— and D M BERGENSTAL Inhibition of Human Mammary and Prostatic Cancers by Adrenalectomy *Cancer Res 12* 134 1952
74 ——— Endocrine Methods of Treatment of Cancer of the Breast *J Nat Cancer Inst 15* 1 1954
75 JACOBS E C Gynecomastia Following Severe Starvation *Ann Int Med 28* 792 1948
76 JESSIMAN A G and F D MOORE Carcinoma of the Breast The Study and Treatment for the Patient *N England J Med 254* 846 1956
77 JUNGCK E C W O MADDOCK C L FEARL *and* C G HELLER Suppression of Urinary Chorionic Gonadotrophin Symptoms and Pulmonary Metastases in Chorionepithelioma by Diethylstilbestrol *Fed Proc 8* 83 1949
78 KULLANDER S *Chorionepithelioma* Treated with Stilbestrol *Lancet 1*·944 1948
79 LACASSAGNE A Apparition de cancers de la mammelle chez la souris male soumise à des injections de folliculine *Compt rend Acad d Sc 195* 630 1932
80 ——— and A RAYNAUD Results obtenus dans l étude de la reaction de l epithelium de la vesicle seminale a la testosterone par l injection de l'hormone dans la lumiere de la glande *Compt rend Soc Biol 126* 579 1937
81 LAIDLAW J C Ketosteroid and Androgen Secretion in Orchiectomized Patients *J Clin Endocrinol 12*·971 1952
82 LAROCHE, G H SIMONNET and J A HUET Contribution a l etude des variations du faux de la folliculine chez la femme *Compt Rend Soc Biol Paris 113* 286 1933
83 LASZLO D A SCHILLING J BELLIN E D GOTTESMAN and C A SCHULMAN Effect of Testosterone on Patients with Bone Metastases *J A M A 148* 1052 1952
84 LATHROP A E C and L LOEB Further Investigations on the Origin of Tumors in Mice III The Part Played by Interval Secretion on Spontaneous Development of Tumors *J Cancer Research 1* 1 1916
85 LEMON H M I S RAVIN J F ROSS J H SISSON T J ANGLEM and A W BRANCA Testosterone Therapy of Metastatic Adenocarcinoma of the Thyroid with Remissions *Cancer 4* 1176 1951
86 LICH R JR and O GRANT Use of Estrogens in Treatment of Bladder Tumors *J Urol 59* 682 1948
87 LOESER A A Male Hormone in Treatment of Cancer of the Breast *Acta Union internat contre cancer 4* 375 1939
88 LOWENHAUPT E and H L STEINBACH Clinical Response of Metastatic Lesions of Carcinoma of the Female Breast to Hormonal Therapy as Related to Histologic Grade of Malignancy *Surg Gynec & Obst 88* 291 1949
89 LUFT R and H OLIVERCRONA Hypophysectomy in Man Experiences in Metastatic Cancer of the Breast *Cancer 8* 261 1955
90 NIGNIN G E R ROTTER and O O MEYER Treatment of Acute Leukemia with Combined Steroid Hormones and Folic Acid Antagonists *Wisconsin M J 52* 120 1953
91 MASON H L and W W ENGSTROM The 17 Ketosteroids Their Origin Determination and Significance *Physiol Rev 30* 321 1950
92 MCCLELLAND J C and G E RICHARDS An Interesting Case of Testicular Tumor *Tr Am A Genito Urin Surgeons 35* 113 1942
93 MCCLURE J A and C C HIGGINS Bilateral Carcinoma of Male Breast After Estrogen Therapy *J.A.M.A 146* 7 1951
94 MCGEE L C The Effect of the Injection of a Lipoid Fraction of Bile Testicle in Capons *Proc Inst Med Chicago 6* 242 1927
95 MORGAN F A 'The Effect of Vitamin Deficiency on Adrenocortical Function *Vitamins and Hormones* New York Academic Press Inc 1951 vol 9 p 161
96 MURPHY W T and H SCHWIPPERT Pituitary Irradiation in Prostatic Cancer *Radiology 56* 376 1951
97 NATHANSON I T and L E TOWNE The Urinary Excretion of Estrogens Androgens and FSH *Following the Administration* of Testosterone to Human Female Castrates *Endocrinol 25* 754 1939
98 NATHANSON I T Effect of Stilbestrol on Advanced Cancer of the Breast *Cancer Res 6* 484 1946
99 ——— Influence of Orchiectomy on Advanced Cancer of the Breast in the Male *Acta Union internat contre cancer 6* 1080 1950
100 ——— Sex Hormones and Castration in Advanced Cancer *Radiology 56* 535 1951

101 ——— and R M Kelly Medical Progress Hormonal Treatment of Cancer *New England J Med 246* 135 180 1952

102 ——— Clinical Investigative Experience With Steroid Hormone in Breast Cancer *Cancer 5* 754 1952

103 ——— *Endocrine Management of Neoplastic Diseases in Glandular Physiology and Therapy* 5th ed Philadelphia J B Lippincott Co 1954 p 478

104 Nesbit R M and W C Baum Endocrine Control of Prostatic Cancer *J A M A 143* 1317 1950

105 Olch J G The Menopausal Age in Women With Cancer of the Breast *Am J Cancer 30* 563 1937

106 Pack G T and H E Ehrlich Neoplasms of the Abdominal Wall With Special Consideration of Desmoid Tumors *Internat Abstr Surg (Surg Gynec & Obst) 79* 177 1944

107 Parkes A S The Adrenal Gonad Relationship *Physiol Rev 25* 203 1945

108 Pearson O H C D West V P Hollander and N E Treves Evaluation of Endocrine Therapy for Advanced Breast Cancer *J.A.M.A 154* 234 1954

109 ——— B S Ray C C Harrold C D West M C Li J P MacLean and M B Lipsett Hypophysectomy in the Treatment of Advanced Cancer *Tr Asso Am Phys 68* 101 1955

110 Peters M V The Influence of Hormone Therapy on Metastatic Mammary Carcinoma *Surg Gynec & Obst 102* 545 1956

111 Pincus G and K V Thimann (eds) *The Hormones Physiology Chemistry and Applications* New York Academic Press Inc 1948 vol 1 p 515 vol 2 pp 471 678

112 Prudente A Postoperative Prophylaxis of Recurrent Mammary Cancer With Testosterone Propionate *Surg Gynec & Obst 80* 575 1945

113 Reifenstein E C Jr and F Albright The Metabolic Effects of Steroid Hormones in Osteoporosis *J Clin Invest 26* 24 1947

114 Ritvo M and N C Peters Regression of Bone Metastases from Breast Cancer After Ovarian Sterilization *Am J Roentgenol 51* 220 1944

115 Rogers J The Menopause *New England J Med 254* 697 750 1956

116 Rusche C Evaluation of Bilateral Orchiectomy in the Treatment of Carcinoma of the Prostate II *Cancer 5* 229 1952

117 Salmon U J Rationale for Androgen Therapy in Gynecology Discussion *J Clin Endocrinol 1* 162 1941

118 Sayers G The Adrenal Cortex and Homeostasis *Physiol Rev 30* 241 1950

119 Schinzinger A Das Karzinoma der Mamma *Munchen med Wchnschr 52* 1724 1905

120 Scott W W and C Vermeulen Studies on Prostatic Cancer Excretion of 17 Ketosteroids Estrogens and Gonadotropins Before and After Castration *J Clin Endocrinol 2* 450 1942

121 Shivers C H de T Bilateral Orchiectomy in Advanced or Recurring Carcinoma of the Bladder With Severe Subjective Symptoms Preliminary Report *J Urol 54* 539 1945

122 Snapper I Castration Combined with Testosterone Treatment After Mastectomy for Breast Cancer *J Mt Sinai Hosp 14* 618 1947

123 Sommers S C and H A Teloh Ovarian Stromal Hyperplasia in Breast Cancer *A M A Arch Path 53* 999 1952

124 Spencer H J Greenberg E Berger M Perrone and D Laszlo Studies on the Effect of Ethylenediaminetracetic Acid in Hypercalcemia *J Clin Lab Med 47* 29 1956

125 Stewart F W Experiences in Spontaneous Regression of Neoplastic Disease in man *Texas Rep Biol & Med 10* 239 1952

126 Swyer A J J S Berger H M Gordon and D Laszlo Hypercalcemia in Osteolytic Metastatic Cancer of the Breast *Am J Med 8* 724 1950

127 Talbot T R and G Escher The Effects of Testosterone Propionate on the Peripheral Blood and Bone Marrow of Women With Advanced Inoperable Carcinoma of the Breast Preliminary Report *J Clin Endocrinol 9* 666 1949

128 Taylor G W Evaluation of Ovarian Sterilization for Breast Cancer *Surg Gynec & Obst 68* 452 1939

129 Taylor S G III J P Ayer and R S Morris Cortical Steroids in the Treatment of Cancer *J.A.M.A 144* 1058 1950

130 ——— and R S Morris Jr Hormones in Breast Metastasis Therapy *M Clin North America* pp 51 61 1951

131 Thorn G W P H Forsham T F Frawley S R Hill M Roche and D L Wilson The Clinical Usefulness of ACTH and Cortisone *New England J Med 242* 824 1950

132 Treves N Castration as a Therapeutic Measure in Cancer of the Male Breast *Cancer 2* 191 1949

133 Trunnell J B B J Duffy Jr V Marshall W F Whitmore and H Q Woodard Use of Progesterone in Treatment of Cancer of Prostate *J Clin Endocrinol 11* 663 1951

134 Ulrich P Testosterone (hormone male) et sone role possible dans le traitement de certains cancers du sein *Acta Union internat contre cancer 4* 377 1939

135 Vass A Occurrence of Uterine Fundus Carcinoma After Prolonged Estrogen Therapy *Am J Obst & Gynec 58* 748 1949

136 Venning E H and J S L Browne Effect of Testosterone on the Excretion of Glycogenic Corticoids *J Clin Endocrinol 7* 729 1947

137 Werner A A The Male Climacteric Report of Two Hundred and Seventy Three Cases *J A M A 132* 189 1946

138 West C D V P Hollander W F Whitmore H T Randall and O H Pearson The Effect of Bilateral Adrenalectomy upon Neoplastic Disease in Man *Cancer 5* 1009 1952

139 White J W The Results of Double Castration in Hypertrophy of the Prostate *Ann Surg 22* 1 1895

140 Woolley G E Fekete and C G Little Effect of Castration in the Dilute Brown Strain of Mice *Endocrinology 28* 34 1941

141 Wyatt J The Effect of Testosterone Propionate on Two Cases of Ovarian Carcinoma *J Obst & Gynec Brit Emp 52* 174 1945

drogenic and Estrogenic Therapy *J Clin Endocrinol 9* 1 1949
61 ——— Hormonal Therapy of Breast Cancer *Am J Roentgenol 63* 326 1950
62 ——— The Effect of Hormonal Imbalance on Advanced Carcinoma of the Male Breast *Ann Surg 133* 191 1951
63 ——— *Unpublished data*
64 HERTZ R The Quantitative Relationship Between Stilbestrol Response and Dietary Folic Acid in the Chick *Endocrinol 37* 1 1945
65 ——— J K CROMER J P YOUNG and B B WESTFALL Observations on the Effect of Progesterone on Carcinoma of the Cervix *in Symposium on Steroids in Experimental and Clinical Practice* Philadelphia Blakiston Co 1951 ch 22 p 365
66 HIRST J C Conservative Treatment and Therapeutic Test for Endometriosis by Androgens *Am J Obst & Gynec 53* 483 1947
67 HORSLEY J S Bilateral Oophorectomy With Radical Operation for Cancer of Breast *Surgery 15* 590 1944
68 ——— Treatment of Cancer of Breast in Premenopausal Patients with Radical Amputation and Bilateral Oophorectomy *Ann Surg 125* 703 1947
69 HUGGINS C and P J CLARK Quantitative Studies of Prostatic Secretion II Effect of Castration and of Estrogen Injection on Normal and on Hyperplastic Prostate Gland of Dogs *J Exper Med 72* 747 1940
70 ——— R E STEVENS JR and C V HODGES Studies on prostatic cancer Effects of Castration on Advanced Carcinoma of Prostate Gland *A M A Arch Surg 43* 209 1941
71 ——— Bilateral Adrenalectomy in Prostatic Cancer Clinical Features and Urinary Excretion of 17 Ketosteroids and Estrogen *Ann Surg 122* 1031 1945
72 ——— Prostatic Cancer Treated by Orchiectomy The Five Year Results *J A M A 131* 576 1946
73 ——— and D M BERGENSTAL Inhibition of Human Mammary and Prostatic Cancers by Adrenalectomy *Cancer Res 12* 134 1952
74 ——— Endocrine Methods of Treatment of Cancer of the Breast *J Nat Cancer Inst 15* 1 1954
75 JACOBS E C Gynecomastia Following Severe Starvation *Ann Int Med 28* 792 1948
76 JESSIMAN A G and F D MOORE Carcinoma of the Breast The Study and Treatment for the Patient *N England J Med 254* 846 1956
77 JUNGCK E C W O MADDOCK C L FEARL and C G HELLER Suppression of Urinary Chorionic Gonadotrophin Symptoms and Pulmonary Metastases in Chorionepithelioma by Diethylstilbestrol *Fed Proc 8* 83 1949
78 KULLANDER S Chorionepithelioma Treated with Stilbestrol *Lancet 1*·944 1948
79 LACASSAGNE A Apparition de cancers de la mammelle chez la souris male soumise a des injections de folliculine *Compt rend Acad d Sc 195* 630 1932
80 ——— and A RAYNAUD Results obtenus dans l etude de la reaction de l epithelium de la vesicle seminale a la testosterone par l injection de l hormone dans la lumiere de la glande *Compt rend Soc Biol 126* 579 1937
81 LAIDLAW J C Ketosteroid and Androgen Secretion in Orchiectomized Patients *J Clin Endocrinol 12*·971 1952
82 LAROCHE G H SIMONNET and J A HUET Contribution a l étude des variations du faux de la folliculine chez la femme *Compt Rend Soc Biol Paris 113* 286 1933
83 LASZLO D A SCHILLING J BELLIN E D GOTTESMAN and C A SCHULMAN Effect of Testosterone on Patients with Bone Metastases *J A M A 148* 1052 1952
84 LATHROP A E C and L LOEB Further Investigations on the Origin of Tumors in Mice III The Part Played by Interval Secretion on Spontaneous Development of Tumors *J Cancer Research 1* 1 1916
85 LEMON H M I S RAVIN J F ROSS J H SISSON T J ANGLEM and A W BRANCA Testosterone Therapy of Metastatic Adenocarcinoma of the Thyroid with Remissions *Cancer 4* 1176 1951
86 LICH R JR and O GRANT Use of Estrogens in Treatment of Bladder Tumors *J Urol 59* 682 1948
87 LOESER A A Male Hormone in Treatment of Cancer of the Breast *Acta Union internat contre cancer 4* 375 1939
88 LOWENHAUPT E and H L STEINBACH Clinical Response of Metastatic Lesions of Carcinoma of the Female Breast to Hormonal Therapy as Related to Histologic Grade of Malignancy *Surg Gynec & Obst 88* 291 1949
89 LUFT R and H OLIVERCRONA Hypophysectomy in Man Experiences in Metastatic Cancer of the Breast *Cancer 8* 261 1955
90 NIGNIN G E R ROTTER and O O MEYER Treatment of Acute Leukemia with Combined Steroid Hormones and Folic Acid Antagonists *Wisconsin M J 52* 120 1953
91 MASON H L and W W ENGSTROM The 17 Ketosteroids Their Origin Determination and Significance *Physiol Rev 30* 321 1950
92 MCCLELLAND J C and G E RICHARDS An Interesting Case of Testicular Tumor *Tr Am A Genito Urin Surgeons 35* 113 1942
93 MCCLURE J A and C C HIGGINS Bilateral Carcinoma of Male Breast After Estrogen Therapy *J A M A 146* 7 1951
94 MCGEE L C The Effect of the Injection of a Lipoid Fraction of Bile Testicle in Capons *Proc Inst Med Chicago 6* 242 1927
95 MORGAN F A The Effect of Vitamin Deficiency on Adrenocortical Function *Vitamins and Hormones* New York Academic Press Inc 1951 vol 9 p 161
96 MURPHY W T and H SCHWIPPERT Pituitary Irradiation in Prostatic Cancer *Radiology 56* 376 1951
97 NATHANSON I T and L E TOWNE The Urinary Excretion of Estrogens Androgens and FSH Following the Administration of Testosterone to Human Female Castrates *Endocrinol 25* 754 1939
98 NATHANSON I T Effect of Stilbestrol on Advanced Cancer of the Breast *Cancer Res 6* 484 1946
99 ——— Influence of Orchiectomy on Advanced Cancer of the Breast in the Male *Acta Union internat contre cancer 6* 1080 1950
100 ——— Sex Hormones and Castration in Advanced Cancer *Radiology 56* 535 1951

101 ——— and R M KELLY Medical Progress Hormonal Treatment of Cancer *New England J Med 246* 135 180 1952

102 ——— Clinical Investigative Experience With Steroid Hormone in Breast Cancer *Cancer 5* 754 1952

103 ——— *Endocrine Management of Neoplastic Diseases in Glandular Physiology and Therapy* 5th ed Philadelphia J B Lippincott Co 1954 p 478

104 NESBIT R M and W C BAUM Endocrine Control of Prostatic Cancer *J A M A 143* 1317 1950

105 OLCH J G The Menopausal Age in Women With Cancer of the Breast *Am J Cancer 30* 563 1937

106 PACK G T and H E EHRLICH Neoplasms of the Abdominal Wall With Special Consideration of Desmoid Tumors *Internat Abstr Surg* (*Surg Gynec & Obst*) *79* 177 1944

107 PARKES A S The Adrenal Gonad Relationship *Physiol Rev 25* 203 1945

108 PEARSON O H C D WEST V P HOLLANDER and N E TREVES Evaluation of Endocrine Therapy for Advanced Breast Cancer *J A M A 154* 234 1954

109 ——— B S RAY C C HARROLD C D WEST M C LI J P MACLEAN and M B LIPSETT Hypophysectomy in the Treatment of Advanced Cancer *Tr Asso Am Phys 68* 101 1955

110 PETERS M V The Influence of Hormone Therapy on Metastatic Mammary Carcinoma *Surg Gynec & Obst 102* 545 1956

111 PINCUS G and K V THIMANN (eds) *The Hormones Physiology Chemistry and Applications* New York Academic Press Inc 1948 vol 1 p 515 vol 2 pp 471 678

112 PRUDENTE A Postoperative Prophylaxis of Recurrent Mammary Cancer With Testosterone Propionate *Surg Gynec & Obst 80* 575 1945

113 REIFENSTEIN E C JR and F ALBRIGHT The Metabolic Effects of Steroid Hormones in Osteoporosis *J Clin Invest 26* 24 1947

114 RITVO M and N C PETERS Regression of Bone Metastases from Breast Cancer After Ovarian Sterilization *Am J Roentgenol 51* 220 1944

115 ROGERS J The Menopause *New England J Med 254* 697 750 1956

116 RUSCHE C Evaluation of Bilateral Orchiectomy in the Treatment of Carcinoma of the Prostate II *Cancer 5* 229 1952

117 SALMON U J Rationale for Androgen Therapy in Gynecology Discussion *J Clin Endocrinol 1* 162 1941

118 SAYERS G The Adrenal Cortex and Homeostasis *Physiol Rev 30* 241 1950

119 SCHINZINGER V Das Karzinoma der Mamma *Munchen med Wchnschr 52* 1724 1905

120 SCOTT W W and C VERMUELEN Studies on Prostatic Cancer Excretion of 17 Ketosteroids Estrogens and Gonadotropins Before and After Castration *J Clin Endocrinol 2* 450 1942

121 SHIVERS C H DE T Bilateral Orchiectomy in Advanced or Recurring Carcinoma of the Bladder With Severe Subjective Symptoms Preliminary Report *J Urol 54* 539 1945

122 SNAPPER I Castration Combined with Testosterone Treatment After Mastectomy for Breast Cancer *J Mt Sinai Hosp 14* 618 1947

123 SOMMERS S C and H A TELOH Ovarian Stromal Hyperplasia in Breast Cancer *A M A Arch Path 53* 999 1952

124 SPENCER H J GREENBERG E BERGER M PERRONE and D LASZLO Studies on the Effect of Ethylenediaminetracetic Acid in Hypercalcemia *J Clin Lab Med 47* 29 1956

125 STEWART F W Experiences in Spontaneous Regression of Neoplastic Disease in man *Texas Rep Biol & Med 10* 239 1952

126 SWYER A J J S BERGER H M GORDON and D LASZLO Hypercalcemia in Osteolytic Metastatic Cancer of the Breast *Am J Med 8* 724 1950

127 TALBOT T R and G ESCHER The Effects of Testosterone Propionate on the Peripheral Blood and Bone Marrow of Women With Advanced Inoperable Carcinoma of the Breast Preliminary Report *J Clin Endocrinol 9* 666 1949

128 TAYLOR G W Evaluation of Ovarian Sterilization for Breast Cancer *Surg Gynec & Obst 68* 452 1939

129 TAYLOR S G III J P AYER and R S MORRIS Cortical Steroids in the Treatment of Cancer *J A M A 144* 1058 1950

130 ——— and R S MORRIS JR Hormones in Breast Metastasis Therapy *M Clin North America* pp 51 61 1951

131 THORN G W P H FORHAM T F FRAWLEY S R HILL M ROCHE and D L WILSON The Clinical Usefulness of ACTH and Cortisone *New England J Med 242* 824 1950

132 TREVES N Castration as a Therapeutic Measure in Cancer of the Male Breast *Cancer 2* 191 1949

133 TRUNNELL J B B J DUFFY JR V MARSHALL W F WHITMORE and H Q WOODARD Use of Progesterone in Treatment of Cancer of Prostate *J Clin Endocrinol 11* 663 1951

134 ULRICH P Testosterone (hormone male) et sone role possible dans le traitement de certains cancers du sein *Acta Union internat contre cancer 4* 377 1939

135 VASS A Occurrence of Uterine Fundus Carcinoma After Prolonged Estrogen Therapy *Am J Obst & Gynec 58* 748 1949

136 VENNING E H and J S L BROWNE Effect of Testosterone on the Excretion of Glycogenic Corticoids *J Clin Endocrinol 7* 729 1947

137 WERNER A A The Male Climacteric Report of Two Hundred and Seventy Three Cases *J A M A 132* 189 1946

138 WEST C D V P HOLLANDER W F WHITMORE H T RANDALL and O H PEARSON The Effect of Bilateral Adrenalectomy upon Neoplastic Disease in Man *Cancer 5* 1009 1952

139 WHITE J W The Results of Double Castration in Hypertrophy of the Prostate *Ann Surg 22* 1 1895

140 WOOLEY G E FEKETE and C G LITTLE Effect of Castration in the Dilute Brown Strain of Mice *Endocrinology 28* 34 1941

141 WYATT J The Effect of Testosterone Propionate on Two Cases of Ovarian Carcinoma *J Obst & Gynec Brit Emp 52* 174 1945

CHAPTER 33

1 BATEMAN J C B MOULTON and N J LARSEN Control of Neoplastic Effusion by Phosphoramide Chemotherapy *A M A Arch Int Med 95* 713 1955
2 BURCHENAL J H R R ELLISON M L MURPHY D A KARNOFSKY M P SYKES T C TAN A C MERMANN M YUCEOGLU W P L MYERS I KRAKOFF and N ALBERSTADT Clinical Studies on 6 mercaptopurine *Ann New York Acad Sc 60* 359 1954
3 Current Status of Hormone Therapy of Advanced Mammary Cancer Report of the Council on Pharmacy and Chemistry *J A M A 146* 471 1951
4 FARBER S L K DIAMOND R D MERCER R F SYLVESTER and J A WOLFF Temporary Remissions in Acute Leukemia in Children Produced by the Folic Acid Antagonist 4 amino pteroyl glutamic Acid (Aminopterin) *New England J Med 238* 787 1948
5 GALTON D A G L G ISRAELS J D N NABARRO and M TILL Clinical Trials of p (di 2-chloroethylamino) phenylbutyric Acid (CB 1348) in Malignant Lymphoma *Brit M J 2* 1172 1955
6 GELLHORN A and V P COLLINS A Quantitative Evaluation of the Contribution of Nitrogen Mustard to the Therapeutic Management of Hodgkin s Disease *Ann Int Med 35* 1250 1951
7 ——— End Results in Lymphosarcoma and Hodgkin s Disease *Proc Third Natl Cancer Conference* Detroit June 4 6 1956 Philadelphia J B Lippincott Co 1957 p 862
8 ——— Objective Criteria in Therapeutic Evaluations *Proc Third Natl Cancer Conference* Detroit June 4 6 1956 Philadelphia J B Lippincott Co 1957 p 436
9 GOLUMBIC C J S FRUTON and M BERGMANN Chemical Reactions of the Nitrogen Mustard Gases I The Transformations of Methyl bis (*B* chloroethyl) Amine in Water *J Org Chem 11* 518 1946
10 HADDOW A and G M TIMMIS Myleran in Chronic Myeloid Leukaemia *Lancet 1* 207 1953
11 HATCH H B J K BRADFORD and A OCHSNER Nitrogen Mustard in Treatment of Advanced Carcinoma of Lung Analysis of One Hundred Ninety-eight Cases *J A M A 160* 1129 1956
12 HITCHINGS G H and G B ELION The Chemistry and Biochemistry of Purine Analogs *Ann New York Acad Sc 60* 195 1954
13 HUGGINS C and C V HODGES Studies on Prostatic Cancer I The Effect of Castration of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate *Cancer Res 1* 293 1941
14 HYMAN G A Studies on Anemia of Disseminated Malignant Neoplastic Disease I The Hemolytic Factor *Blood 9* 911 1954
15 ——— and A GELLHORN Myleran Therapy in Malignant Neoplastic Disease Use of 1 4 dimethanesulfonyloxybutane with Emphasis on Chronic Granulocytic Leukemia *J A M A 161* 844 1956
16 KARNOFSKY D A Triethylene Melamine in the Treatment of Lymphomas and Leukemias *M Clin North America 38* 541 1954
17 KUPFER C Retinoblastoma Treated with Intravenous Nitrogen Mustard *Am J Ophth 36* 1721 1953
18 LAW L W Mechanisms of Resistance and Dependence on Growth of Leukemic Cells *Texas Rep Biol & Med 10* 571 1952
19 ——— Differences Between Cancers in Terms of Evolution of Drug Resistance *Cancer Res 16* 698 1956
20 LEMON H M Cortisone Thyroid Therapy of Metastatic Mammary Cancer *Ann Int Med 46* 457, 1957 Abstr *Proc Am Cancer Res 2* 30 1955
21 NESBIT R M and W C BAUM Endocrine Control of Prostatic Carcinoma *J A M A 143* 1317 1950
22 OSSERMAN E F and D P LAWLER Abnormal Serum and Urine Proteins in 35 Cases of Multiple Myeloma as Studied by Filter Paper Electrophoresis *Am J Med 18* 462 1955
23 PLATZER R F Treatment of Multiple Myeloma *New York J Med 54* 103 1954
24 RANNEY H M and A GELLHORN The Effect of Massive Prednisone and Prednisolone Therapy on Acute Leukemia and Malignant Lymphomas *Am J Med 22* 405 1957
25 REESE A B G A HYMAN G R MERRIAM JR A W FORREST and M M KLIGERMAN Treatment of Retinoblastoma by Radiation and Triethylenemelamine *A M A Arch Ophth 53* 505 1955
26 RHOADS C P (ed) Antimetabolites and Cancer *A A A S* 1955
27 RUNDLES R W and E V CONRAD The Treatment of Multiple Myeloma *Proc Third Natl Cancer Conference* Detroit June 4 6 1956 Philadelphia J B Lippincott 1957 p 389
28 SKIPPER H E A Review On the Mechanism of Action of Certain Temporary Anticancer Agents *Cancer Res 13* 545 1953
29 SYKES M P R W RUNDLES V K PIERCE and D A KARNOFSKY Triethylene Melamine in the Management of Far Advanced Ovarian Cancer *Surg Gynec & Obst 101* 133 1955
30 TREVES N and A I HOLLEB Cancer of the Male Breast A Report of 146 Cases *Cancer 8* 1239 1955
31 ULTMANN J E G A HYMAN and A GELLHORN Chlorambucil in Treatment of Chronic Lymphocytic Leukemia and Certain Lymphomas *J A M A 162* 178 1956

CHAPTER 34

1 ADAIR F E and J B HERRMANN The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast *Ann Surg* 123 1023 1946
2 BEATSON G T On the Treatment of Inoperable Cases of Carcinoma of the Mamma Suggestions for a New Method of Treatment with Illustrative Cases *Lancet 2* 104 162 1896
3 BELL W B Influence of Lead on Normal and Abnormal Cell Growth and on Certain Organs *Lancet 206* 267 1924
4 BISCHOFF F and N R. BLATHERWITH Colloidal Lead Phosphate Substitute for Colloidal Metallic Lead in Cancer Therapy *J Pharmacol and Exper Therap 31* 361 1927
5 BRUNSCHWIG A Observations on the Administration of Large Doses of Calcium in

Metastatic Carcinoma of Bone *Am J Cancer* 25 721 1935

6 ——— *Radical Surgery in Advanced Abdominal Cancer* Chicago University of Chicago Press 1947

7 COLEY W B Cultures of the Streptococcus of Erysipelas *Am J Med Sc* May 1893 p 487

8 ——— The Treatment of Malignant Inoperable Tumors with the Mixed Toxins of Erysipelas and Bacillus Prodigiosus (with a brief report of 80 cases successfully treated with toxins from 1893 to 1914) *Trans Third Internat Conf Cancer Research* Brussels August 1913

9 CRAVER LLOYD F The Nitrogen Mustards Clinical Use *Radiology* 50 486 1948

10 ——— Lymphomas and Leukemias The Value of Early Diagnosis and Treatment *J A M A* 136 244 1948

11 CUTLER MAX Treatment of Advanced Mammary Cancer with Testosterone *J A M A* 138 187

12 DALAND E M An Analysis of Cases at the Pondville Hospital During Its First Two Years *Am J Cancer* 15 2366 1931 a further report *ibid* 21 646 1934

13 ——— Advanced Cancer *J A M A* 136 391 1948

14 DANDY W E Operative Relief from Pain in Lesions of the Mouth Tongue and Throat *A M A Arch Surg* 19 143 1929

15 DAVIS E Disappearance of Carcinomatous Ulceration of Bladder Following Ureterosigmoidostomy Report of two cases *J A M A* 137 450 1948

16 DELARIO A J The Simultaneous Disappearance of Treated and Untreated Tumors after Irradiation *Am J Roentgenol* 60 207 1948

17 DENTON J E and H K BEECHER New Analgesics Council on Pharmacy and Chemistry *J A M A* 141 1051 1146 1949

18 DRESSER R Effect of Ovarian Irradiation on Bone Metastases of Cancer of the Breast *Am J Roentgenol* 35 384 1936

19 DREXLER L S and W E HOWES Ureteral Obstruction in Carcinoma of the Cervix *Am J Obst & Gynec* 28 197 1934

20 DUFFY J J Conservative Procedure in the Care of Surgical Nodes in Intraoral Carcinoma *Am J Roentgenol* 29 241 1933

21 DYER HELEN M *An Index of Tumor Chemotherapy* National Cancer Institute National Institute of Health March 1949

22 ERSKINE ARTHUR W The Management of Advanced Cancer of the Breast *Radiology* 50 7 1948

23 FARBER S Some Observations on the Effect of Folic Acid on Acute Leukemia and Other Forms of Incurable Cancer *Blood* 4 160 1949

24 FOVEAU DE C Les rayons x et le radium en therapeutique gynecologique *Acta radiol* 6 322 1926

25 FRIEDELL H L and J P STORAASLI The Use of Radioactive Phosphorus in the Treatment of Carcinoma of the Breast with Widespread Metastases to Bone *Am J Roentgenol* 64 559 1950

26 HAYDEN R L Hematology *J A M A* 136 308 1948

27 HENCH P S E C KENDALL C H SLOCUMB and H F POLLY The Effect of Hormone of the Adrenal Cortex (17 hydroxy 11 dehydrocorticosterone Compound E) and of Pituitary Adenocorticotropic Hormone on Rheumatoid Arthritis Preliminary report *Proc Staff Meet Mayo Clin* 24 181 1949

28 HENKIN W A Bronchogenic Carcinoma —a Clinical Pathological Study of 36 Autopsied Cases Seen at the Brooklyn Cancer Institute Between 1937 and 1945 inclusive *Ann Int Med* 27 No 2 August 1947

29 HIRSCHBOECK J S M D F LINDERT J CHASE T L CALVY Effects of Urethane in the Treatment of Leukemia and Metastatic Malignant Tumors *J A M A* 136 90 1948

30 HOWES W E and L BERNSTEIN Methods Used and Results Obtained in Treatment of Widespread Metastases Secondary to Mammary Cancer *Radiology* 38 5 1942

31 HUGGINS C Endocrine Control of Prostatic Cancer *Science* 97 542 1943

32 ——— R E STEVENS JR and C V HODGES Studies on Prostatic Cancer Effects of Castration on Advanced Carcinoma of Prostate Gland *A M A Arch Surg* 43 209 1948

33 ——— S T YU and R JONES Inhibitory Effects of Ethyl Carbamate on Prostatic Cancer *Science* 106 147 1947

34 JUDOVICH B D W BATES and K BISHOP Intraspinal Ammonium Salts for the Intractable Pain of Malignancy *Anesthesiology* 5 341 1944

35 KARNOFSKY D A W H ABELMANN L F CRAVER and J H BURCHENAL The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma *Cancer* 1 634 1948

36 LAWRENCE J H R L DOBSON B V A LOW BEER and B R BROWN Chronic Myelogenous Leukemia a Study of 129 Cases in Which Treatment was with Radioactive Phosphorus *J A M A* 136 772 1948

37 LOESER A A Male Hormone in the Treatment of Cancer of the Breast *Acta Unio Internat contra cancrum* 4 375 1939

38 LUSHBAUGH C C J W GREEN JR and J B STORK Histopathologic Study of the Mode of Inhibitions of Cellular Proliferation by Urethane Effects of Urethane on Cellular Proliferation by Urethane Effects of Urethane on Wound Healing *J Nat Cancer Inst* 8 201 1948

39 MEYER W H Depth Dose Calculation *Radiology* 37 476 1941

40 MONIZ E Les possibilities de la chirurgie dans le traitement de certaines psychoses *Lisboa Med* 13 141 1936

41 MURPHY T W and H SCHWIPPERT Pituitary Irradiation in Prostatic Carcinoma Paper delivered before Radiological Soc N A Chicago December 1950

42 MURPHY H H Discussion of Papers on Management of Advanced Cancer *Radiology* 50 19 1948

43 NATHANSON I T Effects of Stilbestrol on Advanced Cancer of the Breast *Cancer Res* 6 484 1946

43a ——— Hormonal Alteration of Advanced Cancer of the Breast *S Clin North America* p 1144 1947

44 PATERSON E A HADDOW I THOMAS and J M WATKINSON Leukemia Treated With Urethane Compared With Deep X Ray Therapy *Lancet* 1 677 1946

45 PATERSON R and H M PARKER Dosage

System for Gamma Ray Therapy *Brit J Radiol* *7* 592 1934

46 PEARSON O H and L P ELIEL Use of Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone in Lymphomas and Leukemias *J A M A* *144* 1349 1950

47 POPPEN J L Prefrontal Lobotomy for Intractable Pain Case Report *Lahey Clin Bull* *4* 205 1946

48 QUIMBY E H Dosage Table for Linear Radium Sources *Radiology* *43* 572 1944

49 REYNOLDS L T LEUCUTIA J C COOK and K E CORRIGAN Colloidal Lead Orthophosphate Associated With Deep Roentgen Therapy in Bone Metastases from Cancer of the Breast *Am J Roentgenol* *60* 193 1948

50 RHOADS C P Nitrogen Mustards in Treatment of Neoplastic Disease *J A M A* *131* 656 1946

51 ROGERS T M Management of Gastric Hemorrhage Using Topical Thrombin *J A M A* *137* 1035 1948

52 SCHINZINGER V Carcinoma mammae *Verhandl deutsch Gesellsch chir* *18* 28 1889 (quoted by Dresser)

53 SCHER J J and W E HOWES Thorium X Treatment of Skin Epithelioma Keratoses and Delayed Radiation Changes *Radiology* *56* 39 1951

54 SNAPPER I The Influence of 2 Hydroxy stilbamidine on the Course of Multiple Myeloma *J Mt Sinai Hosp* (September October) 1948

55 SPURR C L T R SMITH and L O JACOBSON Chemotherapy in Human Lymphomas Leukemias and Allied Disorders of the Hemopoietic System *Radiology* *50* 387 1948

56 SWEET R H Carcinoma of the Esophagus and Stomach *J A M A* *137* 1213 1948

57 ULLMAN H J Combination of Colloidal Lead and Irradiation in Cancer Therapy *J A M A* *89* 1218 1927

58 ULRICH P Testosterone et son role possible dans la traitement de certaines cancers du sein *Acta Unio internat contra cancrum* *4* 377 1939

59 WEBSTER J J Urethane in Leukemia *J A M A* *135* 901 1947

60 WRIGHT CLAUDE STARR Leukemia Polycythemia and Related Diseases *Am J Roentgenol* *64* 907 1950

CHAPTER 35

1 BEST N Radiotherapy and the Nurse *Am J Nursing* *50* 140 1950

2 CAMERON C S Progress in Cancer Research *Am J Nursing* *50* 209 1950

3 COLEMAN M M G PATTERSON H I PITOU and E S WOLF *Nurses' Reference Book* New York Memorial Hospital 1950

4 DERRICKS V and K ROBERTSON Teaching the Patient with a Colostomy *Pub Health Nursing* *41* 16 1949

5 FEAMAN G Better Care for Our Older Patients *Am J Nursing* *48* 702 1948

6 FERGUSON M The Public Health Nurse and the Cancer Program *Pub Health Nursing* *40* 343 1948

7 FRIED E G and K STERN Situation of the Aged Within the Family *Am J Orthopsychiat* *48* 31 1948

8 KELLER C Raising the Cancer Patient's Morale *Am J Nursing* *49* 508 1949

9 LIPKIN, M and J LIPKIN Some Psychosomatic Aspects of the Management of Surgical Patients *Surgery* *25* 268 1949

10 MARTIN H E and E EHRLICH Nursing Care Following Laryngectomy *Am J Nursing* *49* 149 1949

11 NEWTON K Urologic Nursing *Am J Nursing* *50* 167 1950

12 OLMSTEAD L Crutch Walking *Am J Nursing* *45* 28 1945

13 PATTERSON M G Public Health Nursing Aspects of the Care of the Patient With Cancer *Pub Health Nursing* *42* 377 1950

14 SHERFEY M J Psychiatry Belongs at the Bedside *Am J Nursing* *47* 682 1947

15 WATSON S R Nursing Care in Intestinal Obstruction *Am J Nursing* *48* 489 1948

CHAPTER 36

1 AMERICAN COLLEGE OF SURGEONS *Manual for Cancer Programs* 1953

2 BERKSON J The Calculation of Survival Rates *in Carcinoma and Other Malignant Lesions of the Stomach* by W WALTERS H K GRAY J T PRIESTLY *et al* Philadelphia W B Saunders Co 1943 chap 22 p 467

3 ——— and R P GAGE Calculation of Survival Rates for Cancer *Proc Staff Meet Mayo Clin* *25* 270 1950

4 BOAG J W Maximum Likelihood Estimates of Proportion of Patients Cured by Cancer Therapy *J Roy Statist Soc* *11* 15 1949 Series B

5 CLEMMESEN J WHO Subcommittee on Registration of Cases of Cancer as Well as Their Statistical Presentation *Acta radiol* *35* 319 1951

6 HOPKINS C E Absolute Curability of Cancer of the Breast and Statistical Methodology of Evaluation of Follow Up Studies *West J Surg Obst Gynec* *61* 149 1953

7 LEA D E Biological Assay of Carcinogens *Cancer Res* *5* 633 1945

8 MACDONALD E J Criteria for Reporting End Results *Am J Roentgenol* *60* 832 1948

9 MERRELL M Determination of Prognosis Figures in Chronic Disease Baltimore Johns Hopkins University Department of Bio Statistics Paper 238

10 NATHANSON I T and C E WELCH Life Expectancy and Incidence of Malignant Disease Carcinoma of Breast *Am J Cancer* *28* 40 1936

11 ——— and ——— Life Expectancy and Incidence of Malignant Disease Carcinoma of Gastro Intestinal Tract *Am J Cancer* *31* 457 1937

12 ——— and ——— Life Expectancy and Incidence of Malignant Disease Carcinoma of Lip Oral Cavity Larynx and Antrum *Am J Cancer* *31* 238 1937

13 ——— and ——— Life Expectancy and Incidence of Malignant Disease Malignant Lymphoma Fibrosarcoma Malignant Melanoma and Osteogenic Sarcoma *Am J Cancer* *31* 598 1937

14 ——— and ——— Life Expectancy and Incidence of Malignant Disease Carcinoma of

Genito urinary Tract *Am J Cancer 31* 586 1937

15 SMITHERS D W *et al* Cancer of the Breast A Review *Brit J Radiol* Supplement No 4 pp 1 13 1952

16 STOCKS P Estimation of Survival After Treatment 27th Annual Report British Empire Cancer Campaign 1949 p 309

17 TIVEY H Prognosis for Survival in the Leukemias of Childhood Review of the Litera ture and the Proposal of a Simple Method of Reporting Survival Data for These Diseases *Pediatrics 10* 48 1952

18 ——— The Prognosis for Survival in Chronic Granulocytic and Lymphocytic Leuke mia *Am J Roentgenol 72* 68 1954

19 ——— The Natural History of Untreated Acute Leukemia *Ann New York Acad Sc 60* 322 1954

CHAPTER 37

1 BERKSON JOSEPH and R P GAGE Sur vival Curve for Cancer Patients Following Treat ment *J Am Statist A 47* 501 1952

2 BOAG J W Maximum Likelihood Estimates of the Proportion of Patients Cured by Cancer Therapy *J Roy Statist Soc 11* 15 1949

3 FIX EVELYN and JERRY NEYMAN A Simple Stochastic Model of Recovery Relapse Death and Loss of Patients *Human Biol 23* 205 1951

4 GREVILLE T N E *United States Life Tables and Actuarial Tables 1939 1941* Wash ington United States Government Printing Office 1947 143 pp

5 ——— Mortality Tables Analyzed by Cause of Death *The Record* American Institute of Actuaries *37* 283 1948

6 STOCKS PERCY *Cancer Registration in Eng land and Wales an Inquiry Into Treatment and Its Results* Studies on Medical and Population Subjects No 3 London Her Majesty s Stationery Office 1950 p 18

7 WOLFENDEN H H On the Formulae for Calculating the Exposed to Risk in Construct ing Mortality and Other Tables From the In dividual Records of Insured Lives *Tr Actuarial Soc America 43* 234 1942

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